이학석사학위논문

Development of novel Pyrimidine-Embedded Polyheterocycles and Privileged Tetra-Substituted tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione library using Privileged Substructure-Based Diversity-Oriented Synthesis (pDOS)

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Truong Thanh Tung

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Abstract

Development of novel Pyrimidine-Embedded Polyheterocycles and Privileged Tetra-Substituted tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione library using Privileged Substructure-Based Diversity-Oriented Synthesis (pDOS)

Truong Thanh Tung
Department of Chemistry, Organic Chemistry
The Graduate School
Seoul National University

Small molecule libraries play a crucial role in chemical biology, especially, in high-throughput screening. It leads to discovery of new hit to lead compound that potential application in clinical phase. Therefore, library construction strategy is a subject for organic chemist. One of the most famous and important trend is Diversity-oriented Synthesis (DOS) methodology, which was developed by Professor Stuart Schreiber. From the first time introduced, DOS has been proved to be an essential tool in the exploration of chemical and biological space. Our research group has been working on the development of new DOS pathways and library realizations, we proposed a privileged substructure-based diversity-oriented synthesis (pDOS) approach for the efficient generation of distinct polyheterocyclic core skeletons embedded with privileged structure. Continuation of our work, we using pDOS approach for development of new pDOS pathways and construction of small compound libraries for high-throughput screening.

In chapter 1, a new privileged substructure-based diversity-oriented synthesis (pDOS) pathway for the systematic fabrication of polyheterocyclic molecular frameworks with pyrimidine as the key privileged substructure ring have been developed. In this study, we established five pathways to achieve different

pyrimidine-embedded core skeletons from a key intermediate *ortho*-alkynylpyrimidine carbaldehydes with high molecular diversity and positions with potential functionalities for further modification.

In chapter 2, we describe the practical construction of library using solid-phase synthesis with Tetra-Substituted tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione as the core privileged substructure**.** The diversity of this core skeleton was expanded by introduction of at four R- substituted diversity points. As a result, 81 compound libraries were constructed with provide a potential source of for biological screening.

Keywords: Diversity-oriented synthesis, privileged substructure, pyrimidine, polyheterocyclic, N-acyliminium, beta-turn, small molecule libraries, solid-phase.

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I. Chapter 1

Development of Novel Pyrimidine-Embedded Polyheterocycles Pathways Using Privileged Substructure-Based Diversity-Oriented Synthesis (pDOS)

1.1. Introduction

Diversity-oriented synthesis (DOS) aims to synthesize collections of molecules that access the unexplored molecular frameworks with maximum structural and stereochemical diversity for biological screening[1,3]. After 14 years from the first time introduced in the chemical literature by Professor Stuart Schreiber[2], DOS has been proved to be an essential tool in the exploration of chemical and biological space[4-6]. There are many DOS pathways has been developed, it lead to construct of small molecule libraries that are widely distributed in chemical space and, as a result, so many hit compounds has been discovered through biological screening[9-15]

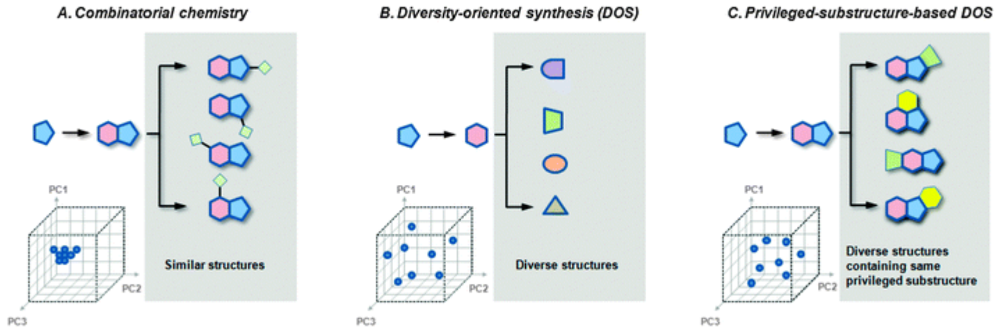


Figure 1: A schematic illustration that compares the synthetic strategies in (A) traditional combinatorial chemistry for the construction of a focused library, (B) a DOS pathway driven by pure complexity-generating reactions, and (C) the pDOS pathway[7]

Privileged structures are important for the efficient discovery of bioactive small molecules. Our research group has been working on the development of new DOS pathways and library realizations, we proposed a privileged substructure-based diversity-oriented synthesis (pDOS) approach for the efficient generation of distinct polyheterocyclic core skeletons embedded with privileged structure, which aims to emphasize the importance of skeletal diversity through the creative reconstruction of privileged substructures embedded in polyheterocyclic molecular frameworks. This is because three-dimensionally discrete core skeletons containing privileged substructures are expected to show high affinity with excellent specificity toward various biopolymers owing to the natural selection process and the evolutionary similarity between gene products[7-16](figure 1).

Continuation of our work, we choose pyrimidine as the key privileged substructure to develop of novel new pDOS pathways. Pyrimidine is a privileged sub-structural motif observed in many bioactive small molecules and drugs such as Antibacterial agents, Urinary tract infections, Thrombus inhibitor, Antipsychotic, and so on[17,18].

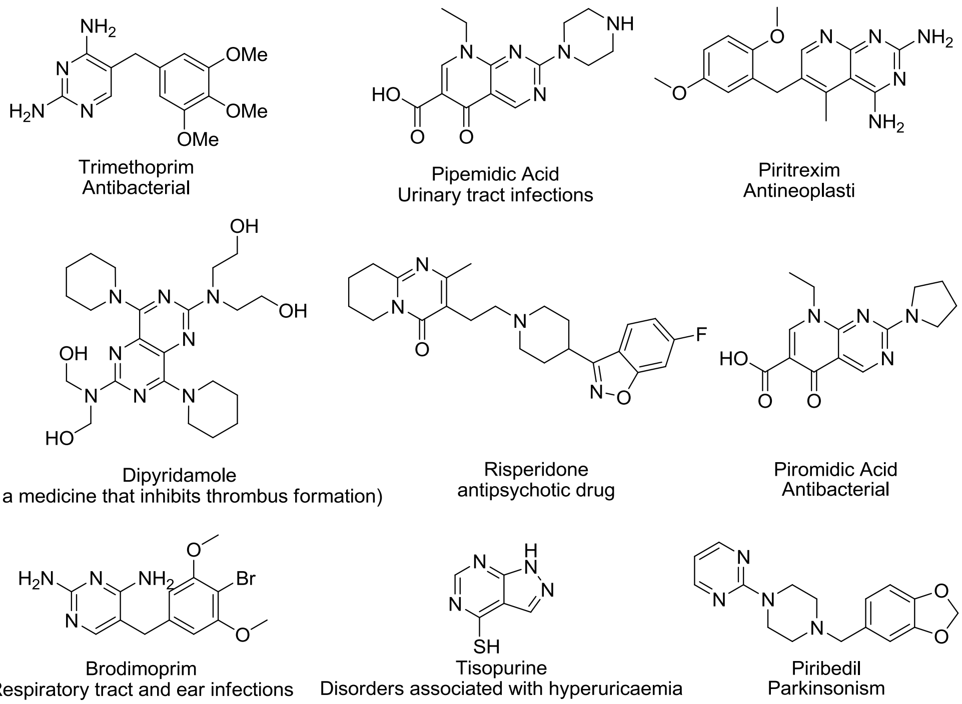


Figure 2: List of pyrimidine and fused pyrimidine marketed drugs

The diversity of scaffold is considered as crucial diversity element, molecule libraries that have three-dimensional structure will have more opportunities to interact with biomacromolecules (because they are three-dimensional structure environments with more or less defined binding regions, pockets, and surfaces, and they will interact only with molecules that have diversity dimensional structure)[19]. As pyrimidine, although a large number of pyrimidine-containing bioactive compounds are synthesized, their structural frameworks are mainly limited to monocyclic or bicyclic skeletons, probably because of the usual design strategy of pyrimidine as nucleoside analogs (Figure 3).

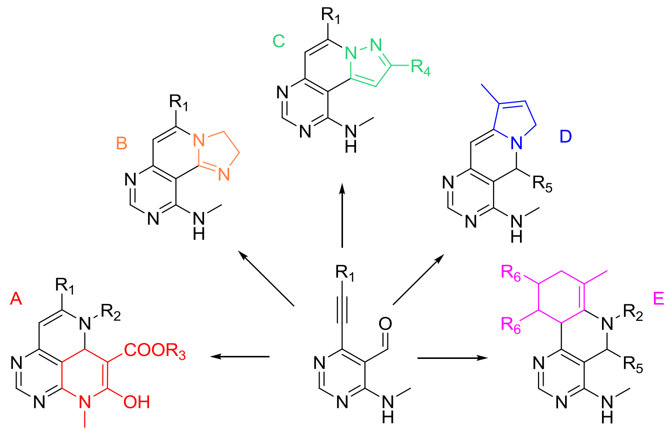


Figure 3: A new diversity-oriented synthesis pathway for the fabrication of a pyrimidine-embedded polyheterocycles library was developed for potential interactions with diverse biopolymers[25]

Herein, we describe a new pDOS strategy for the systematic fabrication of polyheterocyclic molecular frameworks with pyrimidine as the key privileged substructure ring to expand the molecular diversity beyond monocyclic and bicyclic pyrimidine skeletons.

1.2. Results and discussion

A new pDOS strategy has been developed for the systematic fabrication of polyheterocyclic molecular frameworks around a pyrimidine ring. As shown in figure 4, *ortho*-alkynylpyrimidine carbaldehyde[20] have been used as a key intermediate, which can be easily converted to imines or hydrazones, then converted to five different pyrimidine-containing poly heterocycles (A to F) using different reaction condition and coupling partner[20-24] (figure 4).

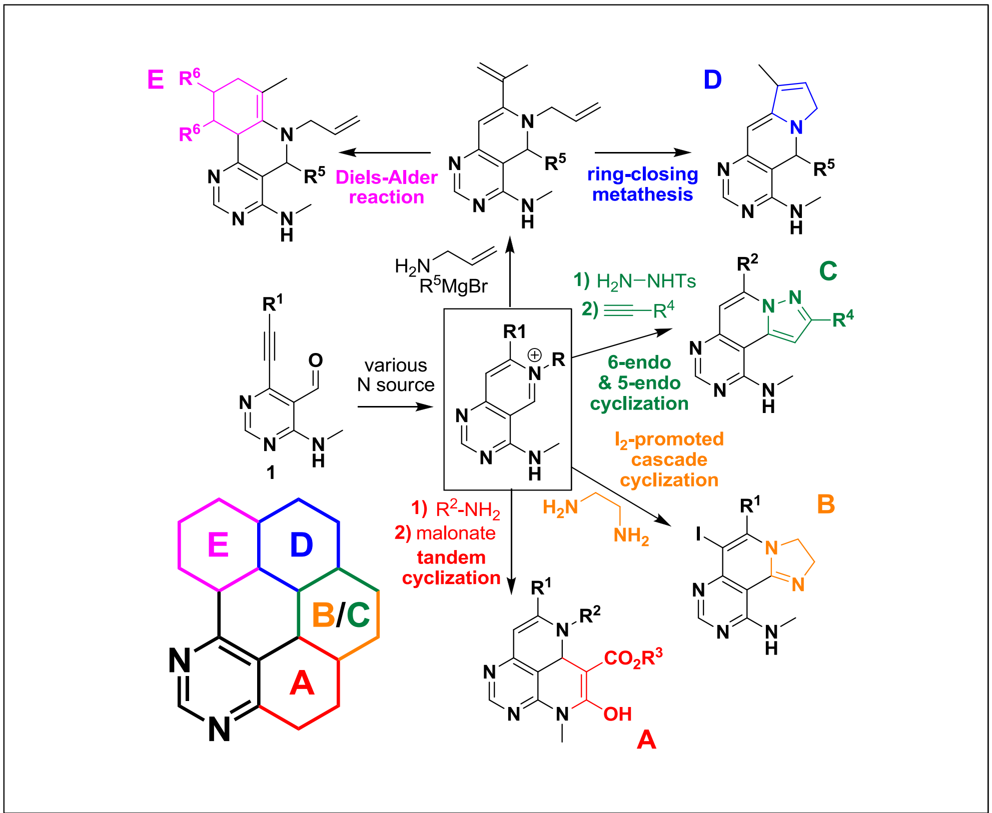


Figure 4: Diversity-oriented synthesis pathways

4-chloro-6-(methylamino)pyrimidine-5-carbaldehyde react with different alkyne via sonogashira coupling to form the key intermediate *ortho*-alkynylpyrimidine carbaldehyde at a high yield (75-90%) . Then, it was reacted with various amines to afford the *ortho*-alkynylpyrimidyl aldimines, followed by Ag-mediated 6-endo cyclization of the imines with the internal alkyne to generate the pyridinium intermediates. Pyridinium intermediates are active compound, which is can be easy reacted with nucleophile to afford nucleophilic addition products. From here, five different pyrimidine-containing poly heterocycles was synthesized[18-19].

To synthesize five different scaffolds, three key intermediate has been prepared by Sonogashira coupling reaction, structure as shown in figure 5 (**1a-c**).

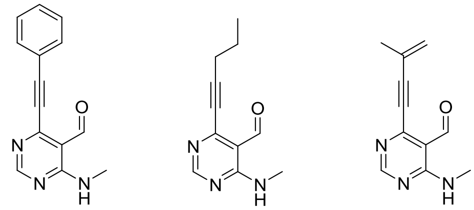
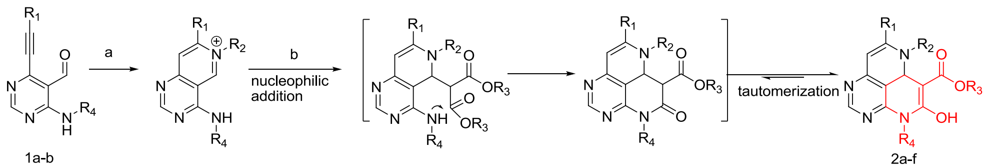


Figure 5: Three key intermediates (**1c** was particular prepared in order to synthesize scaffold D and E)

1.2.1. Pathway A



Condition: a) i: R_2NH2, AcOH, DCE, 80°C. ii: AgOTf, AcOH,DCE, 80°C. b) malonate, BU, DCE, 80°C

Scheme 1: Preparation of scaffold A

First, for the preparation of pathway A (scaffold A) pyridinium intermediates was treated with dialkylmalonates (under base condition) to form nucleophilic addition product and subsequent lactamization of the esters with the methylamine moiety at the C-4 position of the pyrimidine afforded the pyrimidine-containing tricyclic cores.

Then, lactam undergoes tautomerization to form scaffold A. In summary, scaffold A was carried out at in good to excellent yields. The results of synthesis of scaffold A as shown in table 1.

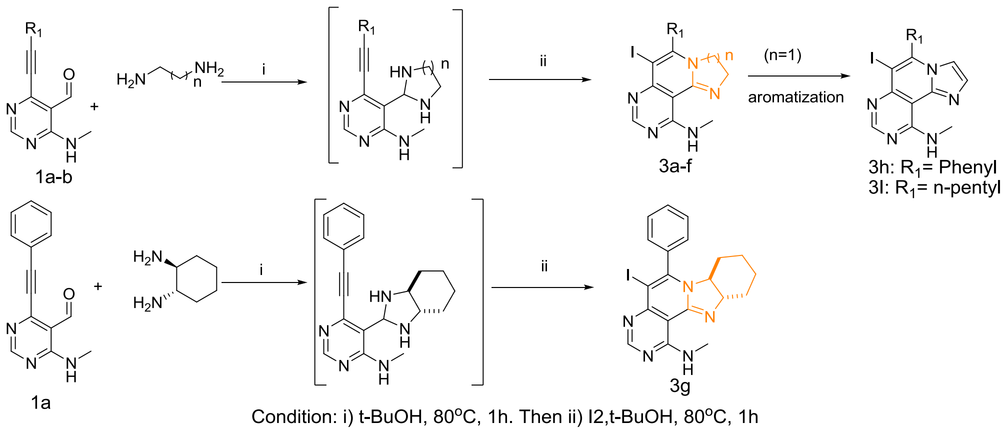
Table 1: Exploration of Scaffold A

Product	R_1	R_2	R_3	R_4	Yield[a] (%)
2a	Phenyl	4-Meo-Ph	Ethyl	Methyl	74
2b	Phenyl	4-Meo-Ph	Methyl	Methyl	70
2c	Phenyl	2-methoxyethyl	Methyl	Methyl	97
2d	n-propyl	4-Meo-Ph	Ethyl	Methyl	84
2e	n-propyl	4-Meo-Ph	Methyl	Methyl	83
2f	n-propyl	2-methoxyethyl	Methyl	Methyl	77

[a]Isolated yields

Scaffold A with four different modifiable substituents at the R_1, R_2, R_3, and R_4 positions and the OH free group are ideally for the DOS's library construction in future.

1.2.2. Pathway B



Condition: i) t-BuOH, 80°C, 1h. Then ii) I2,t-BuOH, 80°C, 1h

Scheme 2: the preparation of scaffold B and expected mechanism

For the preparation of pathway B (scaffold B) *ortho*-alkynylpyrimidine carbaldehyde **1a** and **1b** was treated with diaminoalkanes to afford the cyclic aminal intermediates, then Iodine was added to convert intermediates into scaffold B via tandem cyclization mechanism (Scheme 2). In addition, the Iodo-group is modifiable in the future to expand the molecular diversity via cross coupling reaction such as Sonogashira coupling reaction, Suzuki coupling reaction, Heck reaction and so on. In this one-pot procedure, iodine play as oxidizing agent for the imidazolidine ring formation and also activated the internal alkyne for the 6-endocyclization. The results of synthesis of scaffold B as shown in table 2.

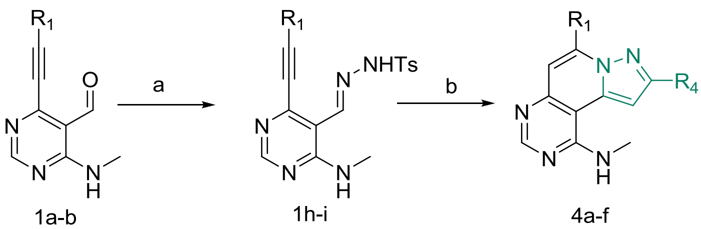
Table 2: Exploration of Scaffold B

Product	$\mathbf{R_1}$	**n**	**Yield[a] (%)**
3a	phenyl	1	60[b]
3b	n-propyl	1	35[c]
3c	phenyl	2	57
3d	n-propyl	2	53
3e	phenyl	3	25
3f	n-propyl	3	39
3g	phenyl	-	47

[a]Isolated yields, [b]Fully aromatized product 3h was obtained in 10% yield, [c]Fully aromatized product 3i was obatined in 34% yield

Due to oxidization condition, compound **3a** and **3b** was converted into the fully aromatized product **3h** and **3i** in 10% and 34% yield, respectively. **3h** and **3i** can be obtained in more than 60% yield if the reaction was stirred overnight.

1.2.3. Pathway C



Condition: a) NH_2NHTs, AcOH, DCE, 80oC, 4h. b) AgOTf, DCE, 80oC, 4h. Then R_4-alkyne, DBU, rt, 2h

Scheme 3: the preparation of scaffold C

For the preparation of scaffold C, *ortho*-alkynylpyrimidine carbaldehyde **1a** and **1b** was treated with tosylhydrazine instead of amine to afford hydrazone intermediates **1h** and **1i**. Then, it has been converted to pyridinium intermediates via Ag-mediated

6-endo cyclization of the hydrazone, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed nucleophilic addition of R_4-containing terminal alkynes Subsequent intramolecular 5-endo cyclization and aromatization afforded scaffold C. The results of synthesis of scaffold C was shown in table 3.

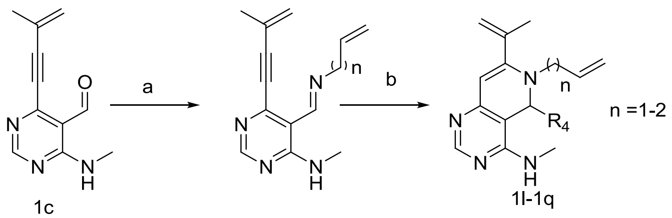
Table 3: Exploration of Scaffold C

Product	R_1	R_4	Yield[a]
4a	Phenyl	Phenyl	64
4b	Phenyl	Cyclopropyl	72
4c	Phenyl	1-methylethenyl	51
4d	n-propyl	Phenyl	70
4e	n-propyl	cyclopropyl	69
4f	n-propyl	1-methylethenyl	69

[a]Isolated yields

1.2.4. Pathway D and E

Scaffold D and E sharing the important intermediate **1c** (a vinyl group at the R_1 position of key substrate). **1c**, then, was reacted with allylic or homoallylic amines to afford ortho-alkynyl aldimines (**1j–1k**), which were diversified by nucleophilic addition with three different Grignard reagents (scheme 4).

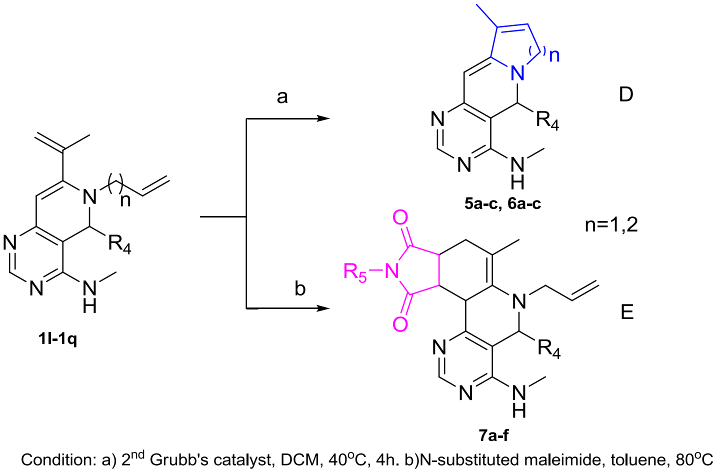


Condition: a) allylic or homoallylic, AcOH, DCE, 80oC, 2h. b) AgOTf, DCE, 80oC, 2h. then R_4MgBr, THF, rt, 2h

Scheme 4: the preparation of key intermediates **1l-1q**

Scaffolds D was synthesized by using ring-closing metathesis (RCM) with Grubbs' second-generation catalyst. The key intermediates **1l**–**1n** were converted to **5a-5c**, fused with 5-membered rings and **1o**–**1q** were converted to **6a-6c,** fused with 6-

membered rings. Scheme 5, table 4.



Scheme 5: the preparation of key intermediates **1l-1q**

By using Diels–Alder reaction of the diene moiety in intermediates **1l–1n** with N-substituted maleimides, six pyrimidine-containing tetracycles **7a–7f** was synthesized (Scaffolds E) as enantiomers in moderate yields. Scheme 5, table 4.

Table 4: Exploration of Scaffold D&E

Product	**SM**	**n**	**R_4**	**R_5**	**Yield[a]%**
5a	1l	1	Methyl	-	50
5b	1m	1	Phenyl	-	48
5c	1n	1	4-MeO-Ph	-	48
6a	1o	2	Methyl	-	48
6b	1p	2	Phenyl	-	60
6c	1q	2	4-MeO-Ph	-	52
7a	1l	1	Methyl	Phenyl	36
7b	1m	1	Phenyl	Phenyl	32
7c	1n	1	4-MeO-Ph	Phenyl	42
7d	1l	1	Methyl	4-MeO-Ph	34
7e	1m	1	Phenyl	4-MeO-Ph	36
7f	1n	1	4-MeO-Ph	4-MeO-Ph	32

[a]Isolated yields

In summary, we established five pathways to achieve different pyrimidine-embedded core skeletons from a key intermediate *ortho*-alkynylpyrimidine carbaldehydes with high molecular diversity and positions with potential functionalities for further modification.

1.2.5. Chemoinformactics study

In order to demonstrated the diverse orientation of our pDOS pathways, we performed the principal moment of inertia (PMI) analysis using PreADMET 2.0 (BMDRC, Korea) and visualized with three principal components calculated using SAS 9.1 (SAS institute Inc., USA) to capture the shape-based distribution of small molecules as dots in an isosceles triangle defined by vertices (0,1), (0.5,0.5), and (1,1), which correspond to the rod, disc, and sphere shapes, respectively.

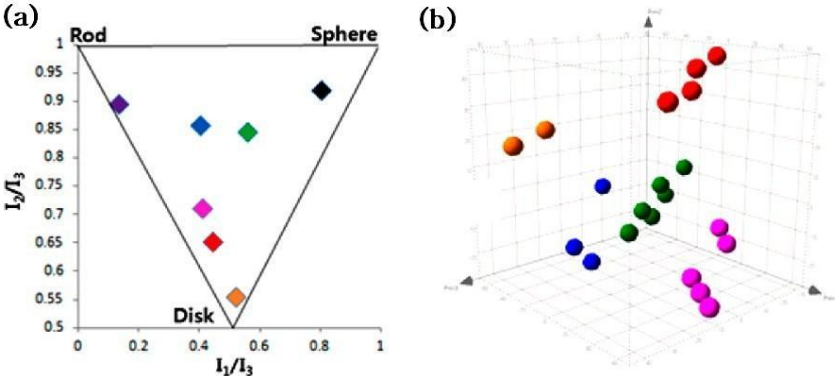


Figure 6: (a) PMI plot depicting five core skeletons in their own color codes along with intermediate 1a and 1l in violet and black colors, respectively; (b) PCA of five different pyrimidine-containing polyheterocycles. Compounds from each skeleton were differently color-coded.

As shown in Figure 6c, five representative scaffolds and two key intermediates were dispersed in the PMI plot, indicating excellent diversity in the shape of each scaffold. Along with shape differences, we clearly visualized that the resulting five color-coded scaffolds were widely distributed in a 3D chemical space with maximum molecular diversity calculated by using unbiased molecular descriptors and analyzed by principal component analysis (PCA, Figure 6b). The molecular diversity of five different scaffolds was differentiated mainly by the topological polar surface area, van der Waals (VDW) surface area, and VDW volume.

1.3. Conclusion

A new privileged substructure-based Diversity-Oriented Synthesis (pDOS) strategy has been developed with pyrimidine as the privileged substructure[25]. The resulting five scaffolds consist of unique pyrimidine-embedded polyheterocycles fused with different ring sizes and orientations. This pDOS was achived by using very common practical reaction and condition such as silver- or iodine-mediated 6-endo cyclization followed by tandem cyclization with different reactants, RCM, Diels–Alder reaction, which is very efficient for library construction. The molecular diversity of each scaffold was successfully confirmed by a series of computational studies, structural alignment of energy-minimized 3D conformers, shape diversity studies using PMI analysis, and in silico PCA analysis. We are currently using this pDOS strategy for construction small compound libraries and will be reported in due course.

II. Chapter 2

Combinatorial Synthesis of Privileged Tetra-Substituted tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione library using Privileged Substructure-Based Diversity-Oriented Synthesis (pDOS)

2.1. Introduction

The number of possible drug-like molecules has been calculated (10^{62} to 10^{200}) to be astronomic[26-27]. In addition, one of the great challenges in the field of chemical biology is the identification of novel small-molecule modulators that can specifically control the functions of gene products and elucidate the associated signaling pathways. Therefore, construction of small molecule libraries for High-throughput Screening is one of object for synthetic chemist.

The human body is a unity that including the complex of protein networks. Inside the body, each protein are linked by non-covalent interactions, they often activate or inhibit other members that lead to change the certain function. Stimulus signals from outside the cell are mediated of the signaling molecules to the inside of that cell by protein-protein interactions. Therefore, the development of novel small-molecule modulators toward protein-protein interaction has been a key research field of interest. The β-turn is one of the three main secondary structural motifs found in proteins and peptides and occurs where the polypeptide strand reverses direction[28-31]. In addition, beta-turns play a crucial role in the interactions between peptides of proteins and receptors, enzymes, or antibodies[28-31]. In summary, it is an idea to develop library of bicyclic beta-turn mimetics small molecules with aim of discovering potent enzyme inhibitors and peptide hormone agonist and antagonists. The Tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione are peptidomimetric structure with four sites of diversity readily accessible, based on its structure there are many expected biological activity, especially, the β-turn mimetrics incorporating functionality at i to i+3 positions of such compounds are predictable (figure 7).

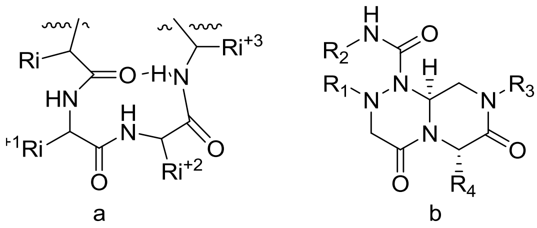


Figure 7: a) β-turn style b) Structure of library compounds

Eguchi et. al. has been working on solid-phase synthesis of bicyclic β-turn peptidomimetics (figure 8)[32-34], which is diversity at the 4 position of compound as shown in figure 6. In our study, one nitrogen atom was introduced in core structure (figure 7b) in order to increase the diversity of library compounds by using various substituted hydrazine.

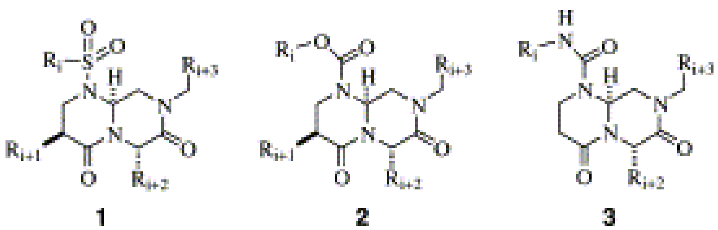
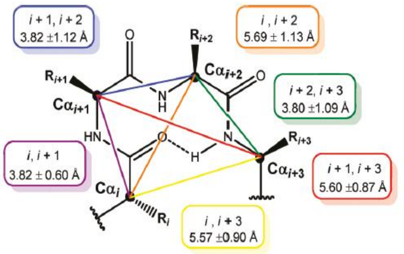
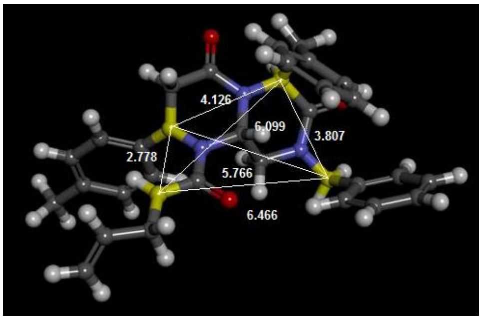


Figure 8: a) Beta-turn style b) structure of library compounds

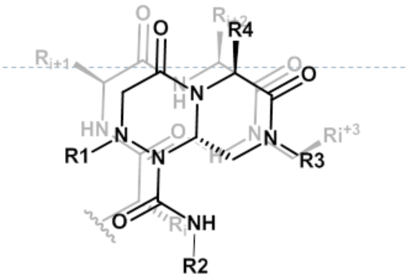
As illustrated in figure 9A, the β-turn consists of four amino acid residues designated from i to i+4 in which the distance between Ci to Ci+3 less than 7 Angstrom. Our designed compounds has been calculated the β-turn mimetic structure by computation analysis in figure 9B, the results show that our compounds are potential beta-turn mimetic structure.



A



B



C

Figure 9: A) Mean and standard deviations of the CR distances taken from a set of 10 245 β-turns in the PDB[15]. B) Distances between substituents in the energy-minimized conformer of targeted compound (using Accelrys discovery studio & Vconf interface) C) Overlap of designed compound and beta-turn structure

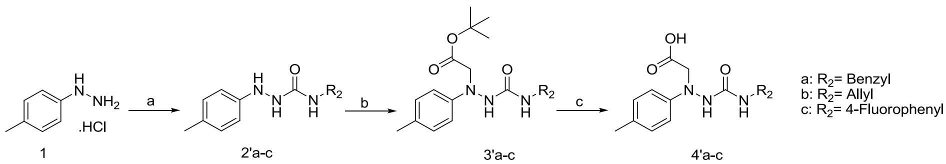
As mentioned previously, β-turn is one of many expected biological activity for these compound that need to be studied in future, therefore, we construct the library compounds to provide a potential source for biological screening.

Herein, we describe a practical synthetic pathway for enantiopure tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione library via solid-phase parallel strategy, it was successfully applied for the construction of 81 library compounds.

2.2. Results and discussion

We initiated the library construction with four different substituents at the R_1, R_2, R_3 and R_4 positions from a single key intermediate (figure 8). To achieve, we are first synthesized three different "2-(1-substitute-2-(substitute-carbamoyl)hydrazinyl) acetic acid" as acid coupling partner and nine amine solid-phase partners to afford 82 library compounds.

2.2.1. Preparation of acid coupling partners:

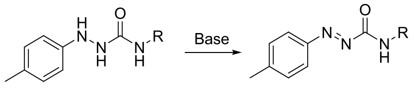


a) R_2-isocyanate, THF, TEA, rt, 4h. b) Bromo tert-butyl ethylacetate, $KHCO_3$, DMF, 80°C, 24h. c) 4N HCl, 1,4-dioxane, rt, 48h.

Scheme 6: preparation of three acid intermediates

As shown in scheme 6, the amine intermediate **2'a-c** could be prepared through different hydrazine and isocyanate. In this work, we choose p-Tolylhydrazine as a fixing part (R_1) and changing isocyanate to effort three types of acid coupling partners. The expanding library with diversity at R_1 position will be reported in due course.

When R_1 is p-Tolyl, due to effect of phenyl group, the compound **2'a-c** could be synthesized from 1 without protection of secondary amine. Then, the intermediate **3'a-c** was obtained from the SN_2 reaction of **2'a-c** with Bromo tert-butyl ethylacetate in basic condition. However, the diazo byproduct always formed at 70 % yield in basic condition via scheme 7.

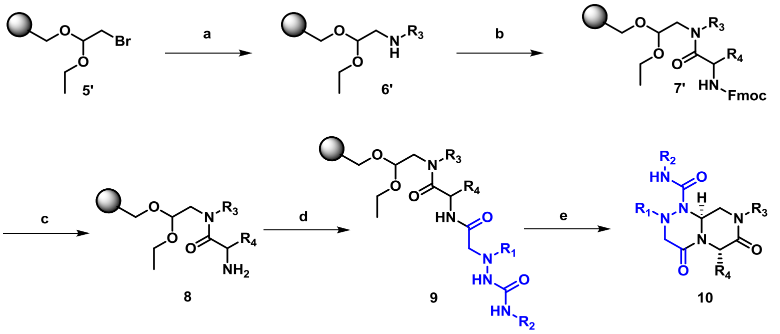


Scheme 7: by-product formation potential in base

Fortunately, among the many conditions tested when using potassium bicarbonate as base in DMF at 80^{o}C, **3’a-c** was obtained successfully with 65-70% yield. Finally, the intermediate **3’a-c** was treated with 4N HCl in 1,4-dioxane for 48h to afford the acid coupling partner **4’a-c** with 70-80 % yield.

2.2.2. Synthesis of tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione via solid phase.

Next, we optimized these synthetic routes in solid phase parallel synthesis format using commercially available bromoacetal resin (loading level 1.8mmol/g). For each final compound 100 mg of resins was used, scheme 8.

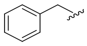
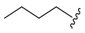
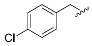
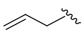
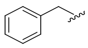
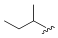


a) R_3-NH2, DMSO, 60¡É, 12h; b) Fmoc-amino acid, HATU, DIPEA, DMF, rt, 4h; c) 20% piperidine, DMF, rt, 10min; d) Acid coupling partner (4') , HOBt, DIC, DMF, rt, 3h; e) formic acid, rt, 18h

Scheme 8: Synthesis of tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione via solid phase**.**

First, resin was treated with a number of primary amines (R_3 group) gave the corresponding secondary amine **6’** by the displacement of the bromide. Then, it was coupled with nine Fmoc-α-amino acids (R_4 group) using HATU, DIPEA in DMF. Fmoc-protection group was removed by treated **6’** with 20% piperidine in DMF, followed by coupling with acid coupling partner (which prepared above) afforded **9.** Finally, product **10** was obtained by cleavage from the resin followed by stereoselective tandem cyclization was achieved by treatment with formic acid at room temperature. The products **10** were observed as the major product by LC-MS and NMR analyses of the crude products. Two representative compounds 10{a,2,9} and 10{b,3,4} were fully characterized using ^{1}H and ^{13}C NMR spectroscopy along with LC/MS analysis, as shown in table 5.

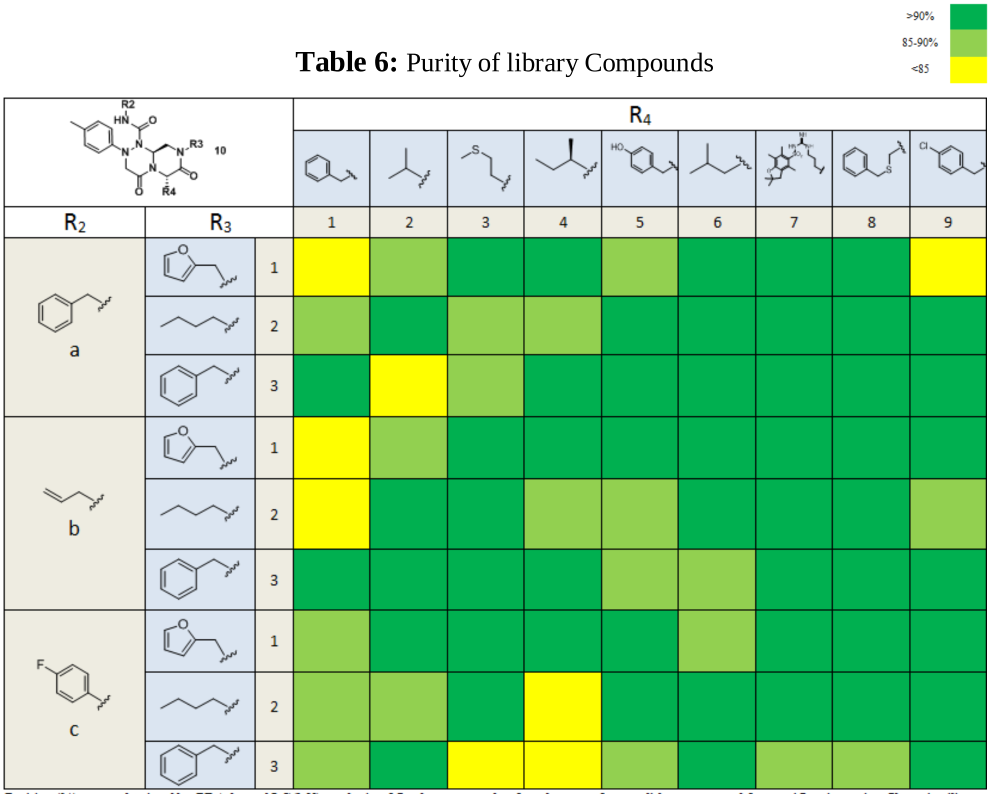
Table 5: Purity and mass of representative Compounds

	R_2	R_3	R_4	Crude Purity[a] (%)	Purity[b] (%)	MS+H Calcd	MS+H found
10{a,2,9}				75	92	574.25	574.22
10{b,3,4}				80	96	490.27	490.09

[a]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after cleavage from solid-support.
[b]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after very fast purification

The purities of all library members were measured using LC/MS equipped with a PDA detector after fast purified by using fast filter via silicagel in syringes, and their average purity was found to be 84%, as shown in table 6.

Table 6: Purity of library Compounds



Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after cleavage from solid-support and fast purification using filter via silica gel in syringe.

The regioselectivity of product as cyclization via N-acyliminium intermediate was studied by various research group, which is only one direction of cyclization by the attaching of Nitrogen atom from the opposite side of the R_4 group[31-36] (figure 10).

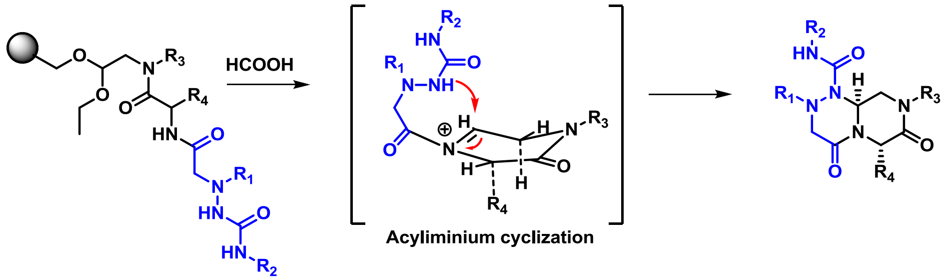


Figure 10: Expected mechanism[31-36]

The N-acyliminium ion formation has been reported in model compounds that allowed only one direction of cyclization[35-36]. We did the computational analysis of N-acyliminium transition state in process of tandem cyclization (using Accelrys discovery studio & Vconf interface), it confimed that the flavord structure lead to attack of Nitrogen atom from the up face compared with R_4 group. Figure 10 and 11.

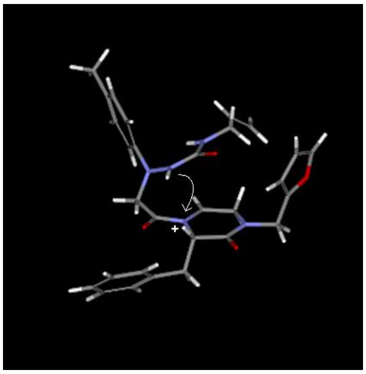


Figure 11: Computational analysis of N-acyliminium transition state

To confirm the structure, we did the crude-LCMS, crude-^{1}H NMR, NOESY, COESY and chiral HPLC for the representative compounds, the resulting shown the bicyclic mimetics as the major product in all cases and only single peak in chiral

HPLC, (see supporting information). 2D-NMR experiments confirm the formation of only a single diastereomer. NOESY of 10{a,2,9} and 10{b,3,4} indicate the compound structure (10{b,3,4} was shown in figure 12) interaction (observed the key NOESY): H5(a) -H31(b), H5(a)-H10(c), in which the hydrogen at the ring junction (H5 or a) is trans to the hydrogen at the 7 (d) position.

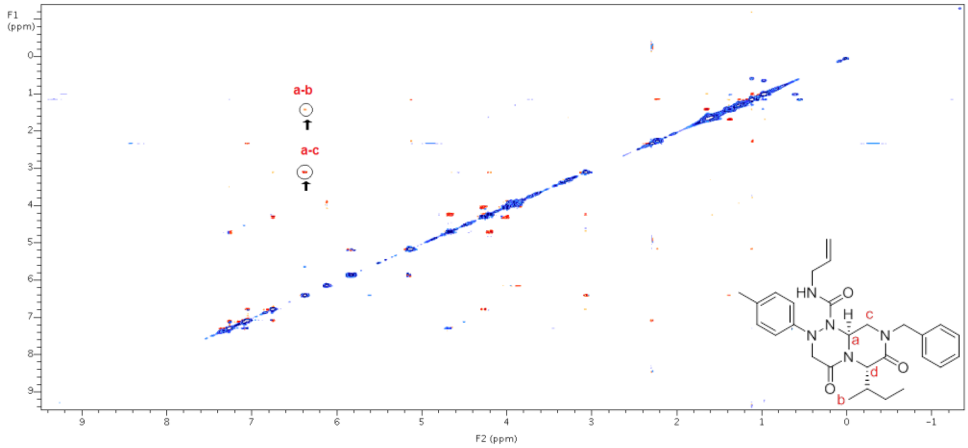


Figure 12: NOESY of 10{b,3,4}

In summary, the 81 compounds of tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione library (R_1 as p-Tolyl by using p-Tolylhydrazine) was synthesized with the diversity of these core skeletons was expanded through the introduction of various substituents at the R_2 (by isocyanate), R_3 (by using amine) and R_4 (by using amino acid) positions from a single key intermediate with an average purity of 84 % on a scale of 100 mg.

2.3. CONCLUSION

We successfully constructed a practical and regioselective synthetic pathway for Privileged enantiopure tetrahydro-1H-pyrazino[2,1-c][1,2,4]triazine-4,7(6H,8H)-dione library via solid-phase parallel strategy. The regioselectivie was achived through the tandem cyclization of N-acyliminium in final step that allowed only one direction of cyclization, which is confirmed by our data including crude-LCMS, crude-NMR, chiral HPLC and computational analysis. The diversity of library was expanded through the introduction of various substituents at the R_2 (by using isocyanate), R_3 (by using amine) and R_4 (by using amino acid) positions from a single key intermediate. This library is currently under biological evaluations process and will be reported in due course.

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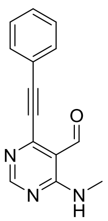
III. EXPERIMENTAL SECTION

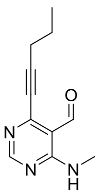
3.1. Experimental section for chapter 1

3.1.1. General synthetic procedure for compounds 1a–1c

To the anhydrous DMF solution (60 mL) of 4-chloro-6-(methylamino)pyrimidine-5-carbaldehyde (1.0 g), $Pd(PPh_3)_2Cl_2$ (5 mol%), and CuI (20 mol%), terminal alkynes (2.0 equiv.) and triethylamine (1.6 mL, 2.0 equiv.) were added under argon atmosphere. After being stirred at room temperature for 4 h, the reaction mixture was quenched with deionized water (200 mL). The resultant was extracted with EtOAc (100 mL × 3) and combined organic layer was washed with brine (100 mL). After drying with anhydrous Na_2SO_4(s), the solvent was removed under the reduced pressure. The residue was purified by silica-gel flash column chromatography to obtain **1a–1c**.

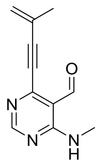


Compound 1a: Yield: 79.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.91 (brs, 1H), 8.67 (s, 1H), 7.65–7.62 (m, 2H), 7.47–7.38 (m, 3H), 3.14 (d, J = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 161.5, 160.4, 155.0, 132.4, 130.3, 128.6, 120.6, 98.3, 83.8, 27.4; LRMS (ESI) *m/z* calcd for $C_{14}H_{11}N_3O$ $[M+H]^+$: 238.09; Found: 237.99.



Compound 1b: Yield: 80.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.86 (s 1H), 8.60 (s, 1H), 3.11 (d, J = 5.2 Hz, 3H), 2.50 (t, J = 6.8 Hz, 2H), 1.72–1.66 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 161.4, 160.4, 155.5, 111.9, 101.3, 76.0, 27.3, 21.5, 21.4, 13.6; LRMS (ESI) *m/z* calcd for $C_{11}H_{13}N_3O$ $[M+H]^+$: 204.11; Found: 204.02.

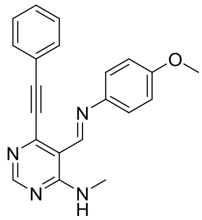
Compound 1c: Yield: 30.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.88 (brs, 1H), 8.63 (s, 1H), 5.64–5.63 (m, 1H), 5.54–5.53 (m, 1H), 3.13 (d, J = 4.8 Hz, 3H), 2.03 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ



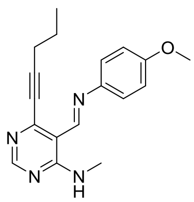
192.6, 161.4, 160.4, 154.9, 126.6, 125.2, 111.8, 99.2, 82.6, 27.4, 22.6; LRMS (ESI) *m/z* calcd for $C_{11}H_{11}N_3O$ $[M+H]^+$: 202.09; Found: 201.84.

3.1.2. General synthetic procedure for compounds 1d–1i

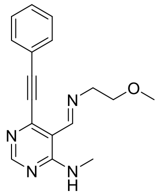
To a dichloroethane (DCE) solution of **1a–1c** (3.0 mmol), amine (5.0 equiv.) or tosylhydrazine (5.0 equiv.), Na_2SO_4, and AcOH were added. After stirring at 80 ^oC until starting materials were consumed, the reaction mixture was quenched with deionized water. The resultant was extracted with dichloromethane (DCM) twice and dried with anhydrous Na_2SO_4(s). After the solvent was removed under the reduced pressure, the residue was purified by silica-gel flash column chromatography to obtain **1d**–**1i**.



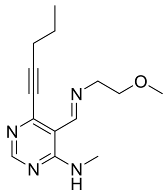
Compound 1d: Yield: 84%; ^1H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.18 (s, 1H), 8.58 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 3H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 3.85 (s, 3H), 3.18 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.78, 158.61, 156.3, 150.5, 143.5, 132.1, 129.8, 128.5, 122.3, 121.3, 114.6, 112.1, 97.0, 85.1, 55.5, 27.5; LRMS (ESI) *m/z* calcd for $C_{21}H_{18}N_4O$ $[M+H]^+$: 343.15; Found: 343.00.



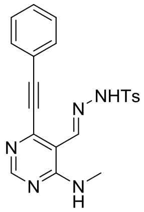
Compound 1e: Yield: 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (d, *J* = 4.4 Hz, 1H), 9.08 (s, 1H), 8.52 (s, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.95 (d, *J* = 6.8 Hz, 2H), 3.85 (s, 3H), 3.15 (d, *J* = 4.8 Hz, 3H), 2.49 (t, *J* = 6.8 Hz, 3H), 1.73–1.64 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.6, 158.5, 156.8, 151.2, 143.6, 122.3, 114.5, 111.9, 99.6, 76.8, 55.5, 27.4, 21.6, 21.5, 13.6; LRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_4O$ $[M+H]^+$: 309.16; Found: 309.06.



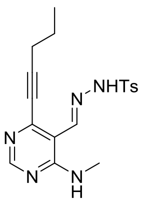
Compound 1f: Yield: 84.6%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (brs, 1H), 8.97 (s, 1H), 8.55 (s, 1H), 7.62–7.60 (m, 2H), 7.42–7.36 (m, 3H), 3.84 (t, *J* = 5.2 Hz, 2H), 3.71 (t, *J* = 5.2 Hz, 2H), 3.4 (s, 3H), 3.11 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 160.5, 158.4, 150.4, 111.3, 99.0, 77.1, 72.2, 61.0, 58.9, 27.2, 21.6, 21.5, 13.6; LRMS (ESI) *m/z* calcd for $C_{17}H_{18}N_3O$ $[M+H]^+$: 295.15; Found: 295.00.



Compound 1g: Yield: 92.3%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (brs, 1H), 8.86 (s, 1H), 8.48 (s, 1H), 3.80 (t, *J* = 5.0 Hz, 2H), 3.69 (t, *J* = 5.0 Hz, 2H), 3.39 (s, 3H), 3.08 (d, *J* = 4.5 Hz, 3H), 2.47 (t, *J* = 7.0 Hz, 2H), 1.71–1.66 (m, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHZ, $CDCl_3$) δ 161.8, 160.5, 158.4, 150.4, 111.3, 99.0, 77.1, 72.2, 61.0, 58.9, 27.2, 21.6, 21.5, 13.6; LRMS (ESI) *m/z* calcd for $C_{14}H_{20}N_4O$ $[M+H]^+$: 261.16; Found: 261.05.



Compound 1h: Yield: 60.3%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.38 (s, 2H), 7.83 (d, *J* = 6.8 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.12–7.06 (m, 4H), 3.04 (d, *J* = 5.2 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.5, 147.9, 145.5, 144.6, 135.1, 131.7, 129.8, 129.7, 128.1, 127.8, 120.5, 110.2, 97.7, 84.2, 27.7, 21.6; LRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_5O_2S$ $[M+H]^+$: 406.13; Found: 405.93.

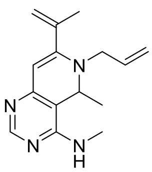


Compound 1i: Yield: 37.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.46–8.43 (s, 2H), 8.42 (s, 1H), 7.81 (d, *J* = 6.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 3.08 (d, *J* = 5.2 Hz, 3H), 2.43 (s, 3H), 2.18 (t, *J* = 7.2 Hz, 2H), 1.46–1.37(m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.7, 149.0, 145.9, 144.7, 135.0, 129.8, 127.7, 109.9, 100.2, 76.4, 27.7,

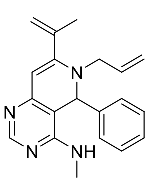
21.6, 21.4, 21.3, 13.5; LRMS (ESI) *m/z* calcd for $C_{18}H_{21}N_5O_2S$ $[M+H]^+$: 372.14; Found: 371.93.

3.1.3. General synthetic procedure for compounds 1j–1o

To a DCE solution of 5-((allylimino)methyl)-*N*-methyl-6-(3-methylbut-3-en-1-yn-1-yl)pyrimidin-4-amine (2.0 mmol) or 5-((but-3-en-1-ylimino)methyl)-*N*-methyl-6-(3–methylbut-3-en-1-yn-1-yl)pyrimidin-4-amine (2.0 mmol), AgOTf (10 mol%) was added. After stirring at 80 °C for 2 h, the reaction mixture was filtered under Na_2SO_4 pad and washed with DCM. After the removal of solvent under the reduced pressure, anhydrous THF was added under argon atmosphere. Then, Grignard reagent was added and stirred at room temperature for 2 h. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted twice with DCM. After drying with anhydrous Na_2SO_4(s), the solvent was removed under the reduced pressure. The residue was purified by silica-gel flash column chromatography to obtain **1j–1o**.

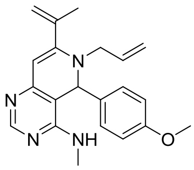


Compound 1j: Yield: 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 5.72–5.65 (m, 1H), 5.64 (s, 1H), 5.30 (t, *J* = 2.0 Hz, 1H), 5.16 (t, *J* = 3.2 Hz, 1H), 5.12–5.10 (m, 1H), 5.08 (dd, *J* = 1.6 Hz, *J* = 1.2 Hz, 1H), 5.05 (dd, *J* = 1.2 Hz, *J* = 0.8 Hz, 1H), 4.53 (d, *J* = 4.8 Hz, 1H), 3.71–3.65 (m, 1H), 3.59–3.53 (m, 1H), 2.99 (d, *J* = 4.4 Hz, 3H), 1.90 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.8, 154.8, 153.6, 140.8, 135.2, 117.8, 117.1, 104.6, 102.1, 54.1, 49.1, 28.1, 21.2, 17.1; LRMS (ESI) *m/z* calcd for $C_{15}H_{20}N_4$ $[M+H]^+$: 257.11; Found: 257.07.

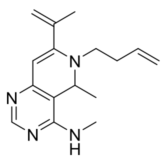


Compound 1k: Yield: 42%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.31 (m, 5H), 5.86–5.73 (m, 1H), 5.31 (s, 1H), 5.25–5.21 (m, 2H), 5.13 (s, 1H), 4.21 (d, *J* = 3.9 Hz, 1H), 3.83

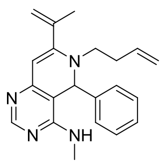
(dd, J = 5.1 Hz, J = 5.1 Hz, 1H), 3.60 (dd, J = 6.6 Hz, J = 6.6 Hz, 1H), 2.94 (d, J = 4.8 Hz, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 156.9, 153.9, 152.7, 134.4, 128.8, 128.4, 126.7, 118.9, 118.2, 117.9, 66.6, 61.6, 56.9, 53.5, 47.1, 28.2, 21.1; LRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_4$ $[M+H]^+$: 319.18; Found: 319.12.



Compound 1l: Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.21 (d, J = 4.8 Hz, 2H), 6.79 (d, J = 3.2 Hz, 2H), 5.81–5.71 (m, 1H), 5.56 (s, 1H), 5.27 (d, J = 6.4 Hz, 1H), 5.23–5.15 (m, 2H), 5.09 (d, J = 2.0 Hz, 1H), 4.19 (d, J = 4.4 Hz, 1H), 3.83–3.77 (m, 1H), 3.75 (s, 3H), 3.59–3.46 (m, 1H), 2.90 (d, J = 4.8 Hz, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.4, 157.3, 155.5, 154.5, 140.7, 134.6, 132.9, 128.0, 118.0, 117.7, 114.0, 101.1, 85.5, 77.3, 56.3, 55.2, 53.3, 28.2, 21.2; LRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_4O$ $[M+H]^+$: 349.20; Found: 349.01.

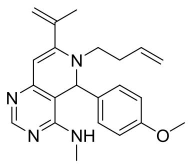


Compound 1m: Yield: 46%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 5.70–5.62 (m, 1H), 5.61 (s, 1H), 5.32 (s, 1H), 5.17 (s, 1H), 4.98 (t, J = 4.5 Hz, 1H), 4.94 (s, 1H), 4.54 (d, J = 4.0 Hz, 1H), 4.28 (dd, J = 6.5 Hz, J = 7.0 Hz, 1H), 4.13 (dd, J = 7.0 Hz, J = 6.5 Hz, 1H), 3.34–3.29 (m, 1H), 3.11 (d, J = 5.0 Hz, 1H), 3.07 (d, J = 3.6, 3H), 2.23–2.18 (m, 2H), 2.05 (s, 1H), 1.95 (s, 3H), 1.27 (t, J = 14.5 Hz, 1H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 156.4, 154.0, 141.1, 134.8, 118.0, 116.9, 104.2, 101.1, 51.6, 50.4, 34.5, 28.1, 21.3, 17.3, 14.2; LRMS (ESI) *m/z* calcd for $C_{16}H_{22}N_4$ $[M+H]^+$: 271.18; Found: 271.07.



Compound 1n: Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.28–7.24 (m, 5H), 5.73–5.63 (m, 1H), 5.57 (s, 1H), 5.28 (dd, J = 0.8 Hz, J = 0.8 Hz, 1H), 5.24 (s, 1H), 5.11–

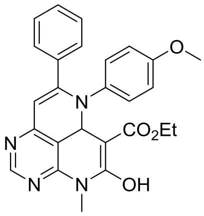
5.10 (m, 1H), 4.99 (dd, J = 1.6 Hz, J = 1.6 Hz, 1H), 4.98–4.97 (m, 1H), 4.95 (t, J = 4.8 Hz, 1H), 4.40 (d, J = 4.4 Hz, 1H), 3.41–3.33 (m, 1H), 3.15–3.08 (m, 1H), 2.95 (d, J = 4.8 Hz, 3H), 2.31–2.25 (m, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.9, 155.3, 154.8, 140.9, 140.8, 134.7, 128.8, 128.4, 126.5, 118.1, 117.1, 103.0, 101.3, 58.2, 51.5, 50.8, 33.7, 29.2, 21.1; LRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_4$ $[M+H]^+$: 333.20; Found: 333.04.



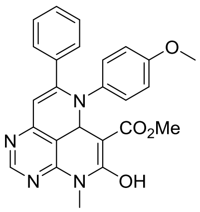
Compound 1o: Yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.18 (d, J = 3.2 Hz, 2H), 6.79 (d, J = 2.8 Hz, 2H), 5.71–5.63 (m, 1H), 5.55 (s, 1H), 5.26 (s, 1H), 5.16 (s, 1H), 5.09 (s, 1H), 4.99–4.98 (m, 2H), 4.95 (s, 1H), 4.21 (d, J = 4.8 Hz, 1H), 3.80 (t, J = 16.4 Hz, 1H), 3.76 (s, 3H), 3.37–3.30 (m, 1H), 3.13–3.05 (m, 1H), 2.94 (d, J = 4.8 Hz, 3H), 2.27 (dd, J = 7.6 Hz, J = 6.0 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.3, 157.3, 155.6, 154.5, 140.9, 134.8, 133.1, 128.7, 127.8, 117.9, 117.0, 114.1, 113.7, 103.3, 101.5, 57.6, 55.2, 51.3, 33.6, 28.2, 21.2; LRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_4O$ $[M+H]^+$: 363.21; Found: 362.98.

3.1.4. General procedure for the preparation of scaffold A (2a−2f)

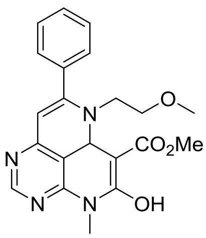
To a DCE solution of **1d–1g** (0.3 mmol), AgOTf (10 mol%) and AcOH (2.0 equiv.) were added. After stirring at 80 °C for 2 h, the reaction mixture was filtered under Na_2SO_4 pad and washed with DCM. After the removal of solvent under the reduced pressure, the reaction mixture was dissolved with dimethylformamide (DMF). 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and dialkylmalonates were added to the solution and stirred at 80 °C for 2 h. The resultant was quenched with deionized water and extracted twice with ethyl acetate (EtOAc). Combined organic layer was washed with brine and dried with anhydrous Na_2SO_4(s). After the solvent was removed under the reduced pressure, the residue was purified by silica-gel flash column chromatography to obtain **2a–2f**.



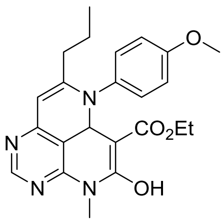
Compound 2a: Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.57 (s, 1H), 8.78 (s, 1H), 8.68 7.42–7.34 (m, 5H), 6.76 (d, *J* = 6.8 Hz, 2H), 6.69 (d, *J* = 6.4 Hz, 2H), 5.85 (s, 1H), 5.43 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.6, 159.8, 157.6, 156.4, 155.2 ,137.9, 136.7, 132.8, 129.5, 128.54, 128.51, 124.7, 121.1, 114.0, 105.4, 92.2, 61.7, 55.4, 28.6, 14.3; HRMS (FAB+) *m/z* calcd for $C_{26}H_{24}N_4O_4$ $[M+H]^+$: 457.1876; Found: 457.1877.



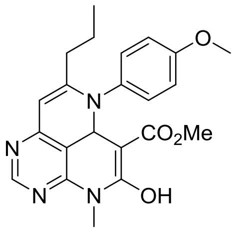
Compound 2b: Yield: 70%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.58 (s, 1H), 8.79 (s, 1H), 8.73 (s, 1H), 7.42–7.36 (m, 5H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 5.86 (s, 1H), 3.96 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 162.6, 159.7, 158.9, 157.7, 156.4, 155.2, 138.4, 136.6, 132.8, 129.5, 128.52, 128.49, 124.7, 120.4, 114.0, 105.3, 92.1, 55.3, 52.6, 28.7; HRMS (FAB+) *m/z* calcd for $C_{25}H_{22}N_4O_4$ $[M+H]^+$:443.1719; Found: 443.1728.



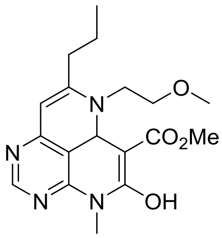
Compound 2c: Yield: 97%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 8.71 (s, 1H), 8.62 (s, 1H), 7.49–7.47 (m, 3H), 7.44–7.42 (m, 2H), 5.55 (s, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.49 (t, *J* = 5.5 Hz, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 163.6, 162.8, 159.9, 157.8, 155.1, 138.6, 136.4, 129.5, 128.6, 127.8, 119.6, 104.5, 89.3, 71.9, 59.0, 52.5, 44.9, 28.6; HRMS (FAB+) *m/z* calcd for $C_{21}H_{22}N_4O_4$ $[M+H]^+$: 395.1719; Found: 395.1728.



Compound 2d: Yield: 84%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.50 (s, 1H), 8.69 (s, 1H), 8.63 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 5.66 (s, 1H), 4.44 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 1.58–1.54 (m, 2H), 1.43 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 164.1, 162.7, 159.9, 157.5, 155.1, 138.4, 127.8, 127.7, 120.2, 115.0, 113.7, 104.2, 87.3, 61.6, 55.9, 28.9, 22.1, 14.4, 14.2; HRMS (FAB+) *m/z* calcd for $C_{23}H_{26}N_4O_4$ $[M+H]^+$: 423.2032; Found: 423.2031.



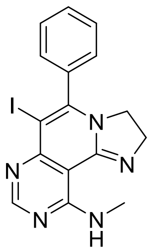
Compound 2e: Yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.73 (s, 1H), 8.63 (s, 1H), 7.13 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 5.66 (s, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 1.59–1.54 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHZ, $CDCl_3$) δ 165.8, 164.2, 162.7, 159.8, 157.7, 157.5, 155.1, 138.8, 138.6, 131.3, 127.3, 119.5, 114.4, 104.2, 87.6, 55.5, 52.6, 35.4, 28.6, 22.1, 13.8; HRMS (FAB+) *m/z* calcd for $C_{22}H_{24}N_4O_4$ $[M+H]^+$: 409.1876; Found: 409.1882.



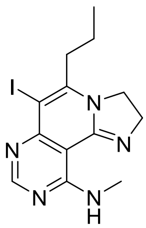
Compound 2f: Yield: 77%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 5.48 (s, 1H), 3.96 (s, 3H), 3.75 (s, 3H), 3.62 (t, J = 5.0 Hz, 2H), 3.57 (t, J = 5.0 Hz, 2H), 3.45 (s, 3H), 2.40 (t, J = 8.0 Hz, 2H), 1.71–1.61 (m, 2H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 165.9, 165.4, 162.7, 160.0, 157.8, 155.1, 138.9, 118.9, 103.8, 86.8, 71.6, 59.1, 52.5, 43.2, 35.8, 29.6, 28.5, 22.0, 14.0; HRMS (FAB+) *m/z* calcd for $C_{18}H_{24}N_4O_4$ $[M+H]^+$: 361.1876; Found: 361.1873.

3.1.5. General procedure for the preparation of scaffold B (3a–3i)

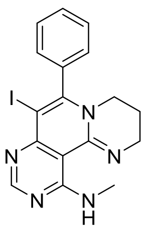
To the *t*–BuOH solution of **1a–1b** (0.4 mmol), diaminoalkane (5.0 equiv.) was added. After stirring at 80 °C for 2 h, iodine (10.0 equiv.) was added to the reaction mixture and stirred at 80 °C for additional 1 h. The reaction mixture was quenched with aqueous sodium thiosulfate solution and extracted twice with DCM. After drying with anhydrous Na_2SO_4(s), the solvent was removed under the reduced pressure. The residue was purified by silica-gel flash column chromatography to obtain **3a**–**3i**.



Compound 3a: Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, *J* = 4.0 Hz, 1H), 8.63 (s, 1H), 7.51 (t, *J* = 7.2 Hz, 3H), 7.30 (d, *J* = 7.2 Hz, 2H), 3.97 (t, *J* = 10.0 Hz, 2H), 3.66 (t, *J* = 10.0 Hz, 2H), 3.13 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 160.4, 157.2, 155.8, 150.8, 138.0, 129.7, 129.0, 127.9, 99.3, 73.2, 52.8, 50.1, 27.6; HRMS (FAB+) *m/z* calcd for $C_{16}H_{14}IN_5$ $[M+H]^+$:404.0372; Found: 404.0370.

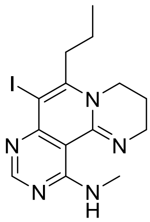


Compound 3b: Yield: 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (brs, 1H), 8.52 (s, 1H), 4.08 (t, *J* = 5.2 Hz, 4H), 3.09 (d, *J* = 5.2 Hz, 3H), 2.78 (t, *J* = 8.0 Hz, 2H), 1.72–1.62 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 160.2, 157.0, 156.1, 151.1, 98.5, 72.9, 52.7, 48.3, 40.3, 29.7, 27.5, 20.8, 14.1; HRMS (FAB+) *m/z* calcd for $C_{13}H_{16}IN_5$ $[M+H]^+$: 370.0529; Found: 370.0526.

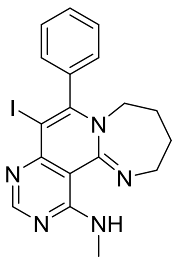


Compound 3c: Yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.53–7.48 (m, 3H), 7.25–7.23 (m, 2H), 3.58 (t, *J* = 5.6 Hz, 2H), 3.46 (t, *J* = 5.6 Hz, 2H), 3.12 (s, 3H), 1.79 (quintet, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.0, 155.0, 151.8, 149.4, 138.9, 129.4, 129.2, 128.5, 103.7, 77.7,

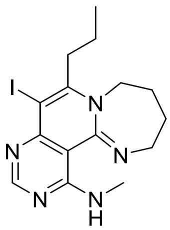
49.6, 43.6, 27.6, 20.9; HRMS (FAB+) *m/z* calcd for $C_{16}H_{14}IN_5$ $[M+H]^+$:418.0529; Found: 418.0526.



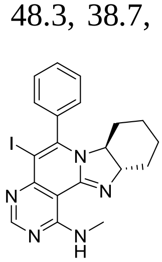
Compound 3d: Yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (brs, 1H), 8.51 (s, 1H), 3.92 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.06 (s, 3H), 2.95 (t, *J* = 8.0 Hz, 2H), 1.95(quintet, *J* = 6.0 Hz, 2H), 1.68–1.58 (m, 2H), 1.09 (t, *J* = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.6, 154.8, 151.2, 149.6, 103.1, 78.3, 46.7, 43.4, 39.3, 27.5, 21.1, 21.0, 14.0; HRMS (FAB+) *m/z* calcd for $C_{14}H_{18}IN_5$ $[M+H]^+$: 384.0685; Found: 384.0688.



Compound 3e: Yield: 25%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.51–7.49 (m, 3H), 7.36–7.39 (m, 2H), 3.91–3.89 (m, 2H), 3.60–3.57 (m, 2H), 3.11 (s, 3H), 1.98–1.92 (m, 2H), 1.67–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 158.7, 155.2, 153.0, 138.1, 129.6, 129.4, 128.6, 104.7, 78.2, 53.3, 48.6, 28.0, 27.7, 26.2, 25.2; HRMS (FAB+) *m/z* calcd for $C_{18}H_{18}IN_5$ $[M+H]^+$: 432.0685; Found: 432.0679.

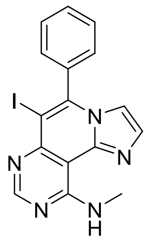


Compound 3f: Yield: 39%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (brs, 1H), 8.53 (s, 1H), 3.91 (t, *J* = 5.6 Hz, 4H), 3.06 (s, 3H), 2.81 (t, *J* = 8.0 Hz, 2H), 1.98 (t, *J* = 3.2 Hz, 4H), 1.75–1.69 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.5, 154.9, 152.9, 152.5, 104.0, 78.3, 50.8, 48.3, 38.7, 29.7, 27.5, 26.2, 25.1, 22.2, 14.1; HRMS (FAB+) *m/z* calcd for $C_{15}H_{20}IN_5$ $[M+H]^+$: 398.0842; Found: 398.0844.

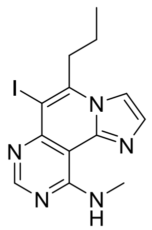


Compound 3g: Yield: 47%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (d, *J* = 4.5 Hz, 1H), 8.83 (s, 1H), 7.59−7.53 (m, 3H), 7.37 (d, *J* = 7.5 Hz, 2H), 3.33 (d, *J* = 5.0 Hz, 3H), 2.81 (t, *J* = 6.5 Hz,

2H), 1.80−1.73 (m, 4H), 1.60−1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.3, 148.0, 143.9, 140.3, 137.6, 130.20, 130.05, 128.3, 122.2, 101.0, 90.4, 28.0, 25.2, 23.5, 23.3, 22.4; HRMS (FAB+) *m/z* calcd for $C_{20}H_{20}IN_5$ $[M+H]^+$: 458.0685; Found: 458.0678.



Compound 3h: Yield: 10%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (brs, 1H), 8.87 (s, 1H), 7.63 (t, *J* = 6.4 Hz, 3H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 1.2 Hz, 1H), 3.33 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 157.8, 149.3, 143.5, 141.3, 136.5, 131.2, 130.1, 129.5, 129.0, 114.0, 101.2, 89.6, 28.0; HRMS (FAB+) *m/z* calcd for $C_{16}H_{12}IN_5$ $[M+H]^+$: 402.0216; Found: 402.0212.

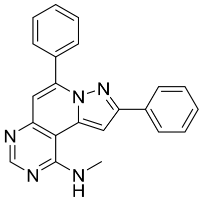


Compound 3i: Yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (brs, 1H), 8.83 (s, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 3.39 (t, *J* = 8.0 Hz, 2H), 3.30 (d, J= 5.2 Hz, 3H), 1.88–1.79 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 157.7, 149.0, 143.9, 141.3, 131.7, 112.1, 100.6, 89.3, 39.6, 28.0, 19.6, 14.1; HRMS (FAB+) *m/z* calcd for $C_{13}H_{14}IN_5$ $[M+H]^+$: 368.0372; Found: 368.0375.

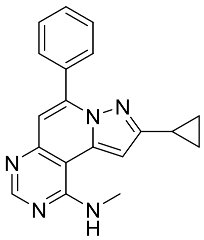
3.1.6. General procedure for the preparation of scaffold C (4a−4f)

To the DCE of **1h–1i** (0.25 mmol), AgOTf (20 mol%) was added. After stirring at 80 ^{o}C for 2 h, the reaction mixture was cooled to room temperature. After the addition of DBU (3.0 equiv.) and terminal alkyne (1.5 equiv.), the reaction mixture was stirred for 2 h. The resultant was quenched with water and extracted with DCM in two times. After drying with anhydrous Na_2SO_4(s), the solvent was removed under the reduced pressure. The residue was purified by silica-gel flash column chromatography to obtain **4a**–**4f**.

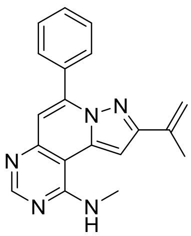
Compound 4a: Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H),



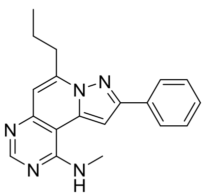
8.00–7.97 (m, 2H), 7.92 (d, *J* = 8.0, 2H), 7.55–7.53 (m, 3H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 5.77 (d, *J* = 5.6 Hz, 1H), 3.29 (d, *J*= 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.8, 153.6, 150.3, 144.8, 136.3, 132.7, 130.0, 129.7, 128.8, 128.7, 128.3, 126.4, 112.6, 103.7, 95.8, 28.7; HRMS (FAB+) *m/z* calcd for $C_{22}H_{17}N_5$ $[M+H]^+$: 352.1562; Found: 352.1556.



Compound 4b: Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.93–7.91 (m, 2H), 7.53–7.49 (m, 3H), 7.05 (s, 1H), 6.47 (s, 1H), 5.69 (d, *J* = 4.8 Hz, 1H), 3.28 (d, *J* = 4.8 Hz, 3H), 2.19–2.13 (m, 1H), 1.07–1.02 (m, 2H), 0.91–0.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 158.3, 156.6, 150.2, 144.6, 135.7, 132.8, 129.9, 129.5, 128.2, 111.6, 103.4, 95.1, 28.7, 9.7, 9.1; HRMS (FAB+) *m/z* calcd for $C_{19}H_{17}N_5$ $[M+H]^+$: 316.1563; Found: 316.1565.

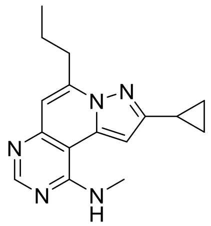


Compound 4c: Yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.00–7.97 (m, 2H), 7.54–7.52 (m, 3H), 7.12 (s, 1H), 6.92 (s, 1H), 5.77 (s, 1H), 5.74 (s, 1H), 5.26 (s, 1H), 3.31 (d, *J* = 5.2 Hz, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 158.3, 156.8, 154.9, 150.3, 144.8, 136.7, 135.8, 132.6, 130.0, 129.7, 128.2, 114.7, 112.4, 103.6, 95.6, 28.7, 20.3; HRMS (FAB+) *m/z* calcd for $C_{19}H_{17}N_5$ $[M+H]^+$: 316.1562; Found: 316.1563.

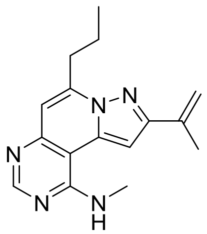


Compound 4d: Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 5.67 (d, *J* = 4.4 Hz, 1H), 3.27 (d, *J* = 4.8 Hz, 3H), 3.18 (t, *J*

= 7.8 Hz, 2H), 1.97–1.87 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.6, 153.3, 150.1, 146.7, 135.4, 132.6, 128.73, 128.71, 126.4, 109.9, 103.1, 95.6, 33.1, 28.6, 19.7, 13.9; HRMS (FAB+) *m/z* calcd for $C_{19}H_{19}N_5$ $[M+H]^+$: 318.1719; Found: 318.1717.



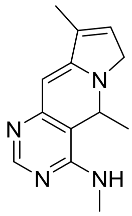
Compound 4e: Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 6.84 (s, 1H), 6.43 (s, 1H), 5.62 (d, *J* = 4.0 Hz, 1H), 3.27 (d, *J* = 4.8 Hz, 3H), 3.15 (t, *J* = 7.6 Hz, 2H), 2.22–2.15(m, 1H), 1.96–1.86 (m, 2H), 1.1–1.07 (m, 5H), 0.96–0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 158.2, 156.5, 146.5, 135.8, 108.9, 102.8, 95.1, 33.1, 28.6, 19.6, 13.9, 9.7, 9.0; HRMS (FAB+) *m/z* calcd for $C_{16}H_{19}N_5$ $[M+H]^+$: 282.1719; Found: 282.1718.



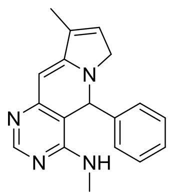
Compound 4f: Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 6.87 (s, 1H), 6.84 (s, 1H), 5.80 (s, 1H), 5.67 (d, *J* = 4.4 Hz, 1H), 5.29–5.28 (m, 1H), 3.28 (d, *J* = 4.8 Hz, 3H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.28 (s, 3H), 1.97–1.87 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.6, 154.6, 150.2, 146.8, 136.8, 134.9, 114.4, 109.8, 103.1, 95.4, 33.1, 28.6, 20.3, 19.7, 13.9; HRMS (FAB+) *m/z* calcd for $C_{16}H_{19}N_5$ $[M+H]^+$: 282.1719; Found: 282.1718.

3.1.7. General procedure for the preparation of scaffold D (5a–5c, 6a–6c)

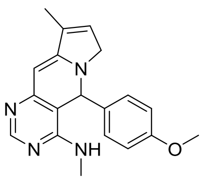
To an anhydrous DCM solution of **1j–1o** (0.1 mmol), second generation Grubb's catalyst (10 mol%) was added under argon atmosphere. After stirring at 40 °C for 2 h, second generation Grubb's catalyst (10 mol%) was added to the reaction mixture and stirred for additional 3 h. After the removal of solvent under the reduced pressure, the residue was purified by silica-gel flash column chromatography to obtain **5a**–**5c** and **6a–6c**.



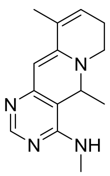
Compound 5a: Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.07 (d, *J* = 2.8 Hz, 1H), 5.06 (dd, *J* = 6.8 Hz, *J* = 7.6 Hz, 1H), 4.6 (s, 1H), 3.97 (d, *J* = 20.8 Hz, 1H), 3.83 (d, *J* = 21.2 Hz, 1H), 3.10 (d, *J* = 4.8 Hz, 3H), 2.07 (s, 3H), 1.52 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 157.9, 156.8, 151.5, 116.3, 113.4, 110.4, 62.2, 48.6, 29.1, 28.3, 23.1, 10.7; HRMS (FAB+) *m/z* calcd for $C_{13}H_{16}N_4$ $[M+H]^+$: 229.1453; Found: 229.1458.



Compound 5b: Yield: 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.56–7.21 (m, 5H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.02 (d, *J* = 2.8 Hz, 1H), 5.88 (s, 1H), 4.48 (s, 1H), 4.06 (s, 2H), 2.90 (d, *J* = 4.8 Hz, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.6, 157.1, 140.0, 129.7, 129.0, 126.9, 121.2, 116.9, 113.5, 110.97, 110.91, 77.6, 76.7, 57.3, 29.2, 28.4, 10.7; HRMS (FAB+) *m/z* calcd for $C_{18}H_{18}N_4$ $[M+H]^+$: 291.1610; Found: 291.1606.

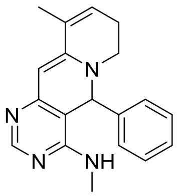


Compound 5c: Yield: 48%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.17 (d, *J* = 9.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.02 (d, *J* = 3.0 Hz, 1H), 5.86 (s, 1H), 4.47 (s, 1H), 4.06 (s, 2H), 3.77 (s, 3H), 2.93 (d, *J* = 4.5 Hz, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.2, 157.5, 142.5, 132.0, 129.1, 115.7, 113.4, 111.0, 107.7, 100.7, 61.8, 51.0, 39.5, 37.2, 29.2, 26.2; HRMS (FAB+) *m/z* calcd for $C_{19}H_{20}N_4$ $[M+H]^+$: 321.1715; Found: 321.1709.

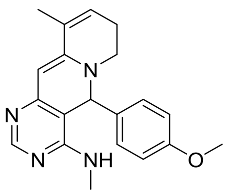


Compound 6a: Yield: 48%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 5.89 (s, 1H), 5.48 (s, 1H), 4.36 (dd, *J* = 11.6 Hz, *J* = 6.4 Hz 1H), 4.30 (s, 1H), 3.34–3.27 (m, 1H), 3.08–3.06 (m, 1H), 3.03 (d, *J* = 3.6 Hz, 3H), 2.33 (d, *J* = 4.0 Hz, 2H), 1.91 (s, 1H), 1.19 (d, *J* =

6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 152.7, 132.3, 130.1, 127.3, 109.9, 94.4, 53.9, 45.1, 29.7, 28.1, 25.0, 18.7, 13.6; HRMS (FAB+) *m/z* calcd for $C_{14}H_{18}N_4$ $[M+H]^+$: 243.1610; Found: 243.1614.



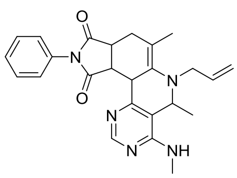
Compound 6b: Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.42–7.40 (m, 2H), 7.32–7.29 (m, 2H), 5.81 (s, 1H), 5.47 (s, 1H), 5.16 (s, 1H), 4.01 (s, 1H), 2.87–2.85 (d, *J* = 4.8 Hz, 3H), 2.82–2.75 (m, 1H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.60, 157.56, 155.7, 147.6, 139.7, 129.8, 129.0, 128.9, 127.2, 104.4, 94.3, 76.7, 63.4, 44.7, 35.6, 35.0, 28.2, 26.97, 26.85, 26.32, 26.29, 26.12, 26.10, 24.7, 18.9; HRMS (FAB+) *m/z* calcd for $C_{19}H_{20}N_4$ $[M+H]^+$: 305.1766; Found: 305.1761.



Compound 6c: Yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.32 (d. *J* = 2.4 Hz, 2H), 6.83 (d, *J* = 2.0 Hz, 2H), 5.81 (s, 1H), 5.46 (s, 1H), 5.14 (s, 1H), 4.53 (s, 1H), 3.96 (s, 3H), 2.86 (d, *J* = 4.8 Hz, 3H), 2.36 (s, 2H), 2.30 (s, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.0, 138.7, 128.5, 127.4, 123.7, 119.0, 114.2, 98.4, 95.7, 76.7, 60.1, 55.1, 48.3, 37.5, 29.7, 28.2, 24.7, 22.9, 21.5; HRMS (FAB+) *m/z* calcd for $C_{20}H_{22}N_4O$ $[M+H]^+$: 335.1872; Found: 335.1875.

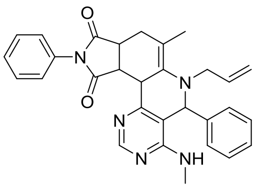
3.1.8. General procedure for the preparation of scaffold E (7a–7f)

To a toluene solution of **1j**–**1l** (0.1 mmol), maleimide (2.0 equiv.) was added. After stirring at 85 ^{o}C for 3 days, organic solvent was removed under the reduced pressure. The residue was purified by silica-gel flash column chromatography to obtain **7a–7f**.

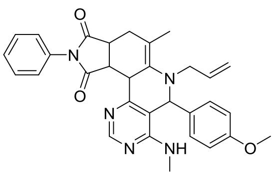


Compound 7a: Yield: 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.41–7.29 (m, 5H), 5.72–5.69 (m, 1H), 5.36 (d, *J* = 6.8 Hz, 1H), 5.21–5.13 (m, 2H),

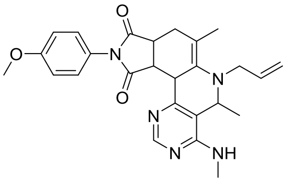
5.06 (s, 1H), 4.27–4.20 (m, 2H), 3.96–3.87 (m, 2H), 3.79–3.75 (m, 1H), 3.70–3.63 (m, 1H), 2.99 (d, J = 4.4 Hz, 3H), 2.96–2.89 (m, 1H), 1.96 (s, 3H), 1.18 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 179.5, 177.0, 157.32, 157.27, 156.2, 156.1, 153.9, 152.3, 139.9, 134.7, 133.1, 129.0, 128.2, 126.78, 126.76, 119.7, 117.4, 117.2, 104.3, 76.7, 53.5, 53.3, 48.9, 48.7, 41.3, 40.3, 37.9, 35.8, 29.7, 28.2, 22.3, 16.4, 16.3; HRMS (FAB+) *m/z* calcd for $C_{25}H_{27}N_5O_2$ $[M+H]^+$: 430.2243; Found: 430.2236.



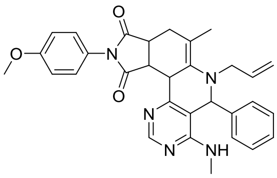
Compound 7b: Yield: 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.75–7.26 (m, 10H), 5.77–5.71 (m, 1H), 5.34 (s, 1H), 5.30–5.26 (m, 2H), 5.23 (s, 1H), 4.09–4.08 (m, 2H), 4.02–3.95 (m, 2H), 3.61–3.55 (m, 1H), 2.94 (m, 1H), 2.91 (d, J = 4.8 Hz, 3H), 2.30 (d, J = 4.8 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 176.7, 158.2, 156.8, 156.7, 153.9, 140.4, 133.9, 133.4, 129.3, 129.0, 128.9, 128.7, 128.2, 128.1, 127.2, 126.9, 126.77, 126.70, 119.2, 118.2, 118.1, 103.4, 56.9, 52.9, 40.4, 37.4, 35.6, 29.7, 28.2, 22.5; HRMS (FAB+) *m/z* calcd for $C_{30}H_{29}N_5O_2$ $[M+H]^+$: 492.2400; Found: 492.2394.



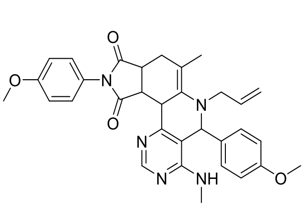
Compound 7c: Yield: 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.50–7.20 (m, 7H), 6.89–6.86 (m, 2H), 5.78–5.74 (m, 1H), 5.35 (s, 1H), 5.33–5.26 (m, 2H), 5.21 (s, 1H), 4.06–4.03 (m, 2H), 3.98–3.96 (m, 2H), 3.81 (s, 3H), 3.63–3.57 (m, 1H), 3.01–2.96 (m, 1H), 2.95 (d, J = 12.0 Hz, 3H), 2.85 (d, J = 4.8 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 177.3, 170.7, 159.7, 159.2, 158.2, 158.0, 156.6, 150.1, 133.9, 132.6, 127.99, 127.86, 118.2, 114.5, 114.36, 114.32, 86.0, 76.7, 64.6, 55.5, 55.3, 40.4, 35.5, 29.7, 28.3, 26.7, 25.0, 17.1; HRMS (FAB+) *m/z* calcd for $C_{31}H_{31}N_5O_3$ $[M+H]^+$: 522.2505; Found: 522.2488.



Compound 7d: Yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.28–7.20 (m, 3H), 6.97–6.93 (m, 1H), 5.74–5.63 (m, 1H), 5.36 (d, *J* = 7.6 Hz, 1H), 5.22–5.13 (m, 2H), 5.05 (s, 1H), 4.27–4.17 (m, 2H), 3.90–3.83 (m, 2H), 3.80 (s, 3H), 3.75–3.63 (m, 2H), 2.93 (d, *J* = 9.6 Hz, 3H), 2.94–2.85 (m, 1H), 1.96 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 159.3, 157.37, 157.33, 156.2, 156.1, 153.9, 152.3, 139.9, 134.8, 127.94, 127.92, 119.7, 117.4, 117.2, 116.4, 114.40, 114.38, 55.48, 55.46, 53.3, 48.9, 48.7, 41.3, 40.3, 37.8, 29.7, 28.20, 28.17, 22.3, 16.4, 16.3; HRMS (FAB+) *m/z* calcd for $C_{26}H_{29}N_5O_3$ $[M+H]^+$: 460.2349; Found: 460.2359.



Compound 7e: Yield: 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.35–7.22 (m, 7H), 6.99–6.97 (m, 2H), 5.75 (m, 1H), 5.35 (s, 1H), 5.35–5.28 (m, 2H), 5.24 (s, 1H), 4.13–4.10 (m, 2H), 4.00 (m, 2H), 3.82 (d, *J* = 5.2 Hz, 3H), 3.62–3.60 (m, 1H), 2.94–2.91 (m, 1H), 2.89 (d, *J* = 4.8 Hz, 3H), 2.84 (d, *J* = 4.8 Hz, 1H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 177.3, 159.3, 158.1, 156.7, 140.4, 134.0, 133.9, 129.3, 129.1, 128.9, 128.7, 127.9, 127.6, 127.2, 126.7, 118.3, 116.4, 114.8, 114.5, 114.4, 114.1, 103.3, 76.7, 55.5, 40.4, 35.5, 29.7, 28.29, 28.26; HRMS (FAB+) *m/z* calcd for $C_{31}H_{31}N_5O_3$ $[M+H]^+$: 522.2505; Found: 522.2502.



Compound 7f: Yield: 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.40–7.16 (m, 4H), 6.98–6.95 (m, 2H), 6.86–6.84 (m, 2H), 5.74–5.73 (m, 1H), 5.32 (d, *J* = 6.0 Hz, 1H), 5.28–5.26 (m, 2H), 5.23 (s, 1H), 4.05–4.00 (m, 2H), 3.96–3.92 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.61–3.55 (m, 1H), 2.95–2.89 (m, 1H), 2.87 (d, *J* = 4.8 Hz, 3H), 2.83 (d,

J = 4.8 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 177.2, 168.2, 159.8, 159.3, 156.6, 151.1, 134.0, 132.6, 128.5, 128.0, 127.9, 118.1, 114.46, 114.40, 60.8, 55.5, 55. 2, 52.6, 40.4, 35.5, 31.9, 31.4, 30.2, 29.7, 28.2, 22.6; HRMS (FAB+) *m/z* calcd for $C_{32}H_{33}N_5O_4$ $[M+H]^+$: 552.2611; Found: 552.2605.

3.1.9. Principal Component Analysis (PCA) Data

3.1.9.1. Eigenvalues of the covariance matrix

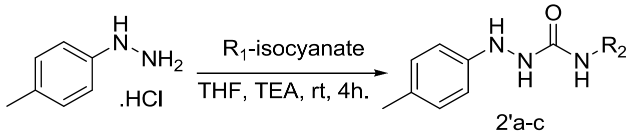
Eigenvalues of the covariance matrix				
	Eigenvalue	Difference	Proportion	Cumulative
Prin 1	1599.23729	1030.25068	0.6138	0.6138
Prin 2	568.98661	265.65905	0.2184	0.8321
Prin 3	303.32756	199.55242	0.1164	0.9485

3.1.9.2. Eigenvectors in principal component analysis

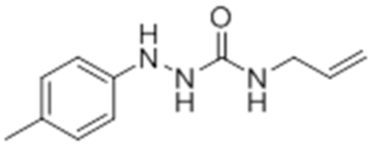
Eigenvectors			
	Prin 1	**Prin 2**	**Prin 3**
Ring Energy	0.304456	0.182719	0.262972
Molecular weight	0.370201	−0.062337	0.347968
Topological PSA	0.454293	0.212850	−0.024271
2D VDW surface	0.405094	−0.093542	0.144375
2D VDW volume	0.394177	−0.145550	0.166564
Fraction of 2D VSA hydrophobic	−0.056418	−0.092711	0.084747
Fraction of 2D VSA polar	0.162504	0.308346	−0.347758
Fraction of 2D VSA Hbond donor	−0.245592	0.817384	0.216717
Fraction of 2D VSA Hbond acceptor	0.389214	0.254489	−0.599958
Charge polarization	0.054814	0.225686	0.474925

3.2. Experimental section for chapter 2

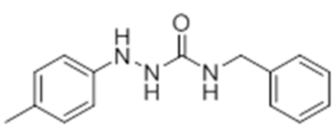
3.2.1. General synthetic procedure for intermediate compounds 2’a-c



A solution of p-tolylhydrazine hydrochloride (10g, 0.063 mol), TEA (8.8 ml, 0.063 mol) in THF (200 ml) was added and a solution of isocyanate (1.0 eqv) in THF was added. After stirring at room temperature for 7 hr until starting material were consumed, the reaction mixture was quenched with deionized water. The resultant was extracted with ethyl acetate (EA) twice and dried with anhydrous Na_2SO_4(s). After the solvent was removed under the reduced pressure, the residue was purified by silica-gel flash column chromatography to obtain **2’a-c**

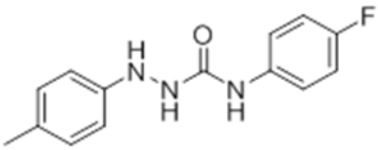


Compound 2’a: Yield: 94%; ^{1}H NMR (500 MHz, DMSO-d6) δ 7.75 (s, 1H), 7.41 (s, 1H), 6.96 (d, 2H, *J*=8Hz), 6.61 (d, 2H, Z=8.5 Hz), 6.53 (s, 1H), 5.74-5.79 (m, 1H), 4.95-5.05 (dd, 2H, J=17 Hz, J=10.5 Hz), 3.63 (s, 2H), 2.16 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ 159.5, 147.6, 137.2, 129.6(2C), 127.8, 114.5, 112.9(2C), 41.6, 20.6; LRMS (ESI) m/z calcd for C11H15N3O [M+1]+:206.12; Found: 206.04.



Compound 2’b: Yield: 91%; ^{1}H NMR (500 MHz, DMSO-d6) δ 7.83 (s, 1H), 7.46 (s, 1H), 7.26-7.28 (m, 3H), 7.18-7.23 (m, 2H), 7.01 (s, 1H), 6.97 (d, *J*=8.5

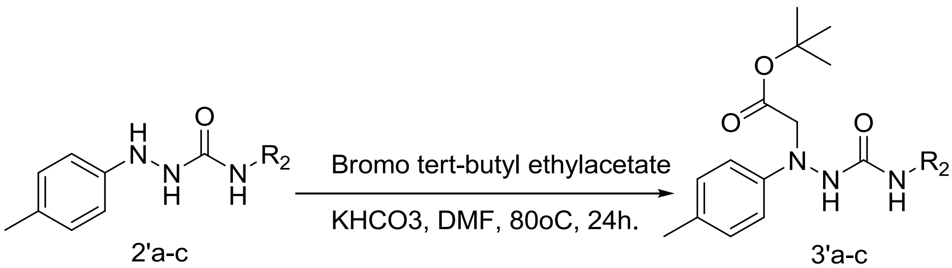
Hz, 2H), 6.64 (d, J=8 Hz, 2H), 4.22 (d, J=6 Hz, 2H), 2.17 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ 159.8, 147.6, 141.5, 129.6(2C), 128.5(2C), 127.8, 127.4(2C) 126.9, 112.9(2C), 42.9, 20.6; LRMS (ESI) m/z calcd for C15H17N3O [M+1]+:256.14; Found: 256.02.



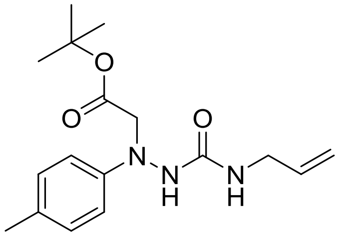
Compound 2'c: Yield: 88%; ^{1}H NMR (500 MHz, DMSO-d6) δ 8.75 (s, 1H), 8.15 (s, 1H), 7.55 (t, *J*=3 Hz, *J*=5.5 Hz, 2H), 7.54 (s, 1H), 7.04 (t, *J*=9 Hz,

J=8.5 Hz, 2H), 6.98 (d, J=8 Hz, 2H), 6.68 (d, J=8.5 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 168.6, 155.9, 147.4, 130.2(2C), 120.3(2C), 116.1(2C), 113.8(2C), 58.9, 43.9, 21.1; LRMS (ESI) m/z calcd for $C_{14}H_{14}FN_3O$ [M+1]+:260.11; Found: 260.00.

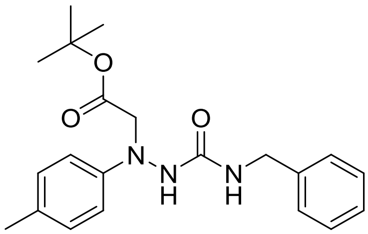
3.2.2. General synthetic procedure for intermediate compounds 3'a-c



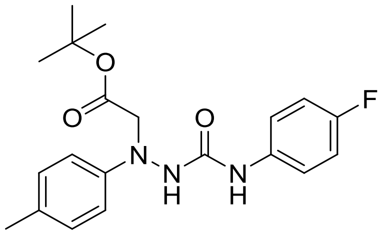
A 500 ml round-bottom-flash was fitted with a glass stopper and reflux condenser. A suspension of **2'a-c** (10g, 1eqv) in 220ml of DMF was added to the flask and then $KHCO_3$ (1 eq), t-Butylbromoacetate (2 eq) was added and stirred at 80^0C for 24h until starting material were consumed. The reaction mixture was filtered and extracted with ethyl acetate (EA) (200ml X 3). The organic solution was washed with Brine (200ml X 3), evaporated and the residue was purified by silica-gel flash column chromatography to obtain **3'a-c**



Compound 3'a: Yield: 68%; ^{1}H NMR (500 MHz, CDCl3) δ 7.07 (d, 2H, *J*=8 Hz), 6.74 (d, 2H, *J*=2 Hz), 6.64 (s, 1H), 6.28 (t, 1H), 5.78-5.84 (m, 1H), 5.03-5.12 (m, 2H), 4.22 (d, 1H, *J*=18 Hz), 3.97 (d, 1H ,*J*=17.5 Hz), 3.83-3.87 (m, 2H), 2.26 (s, 3H), 1.403 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 169.2, 158.1, 145.9, 135.0, 130.4, 129.9(2C), 115.4, 113.3(2C), 82.8, 56.5, 42.0, 28.0(3H), 20.3; LRMS (ESI) *m/z* calcd for $C_{17}H_{25}N_3O_3$ $[M+1]^+$: 320.19; Found: 320.01.

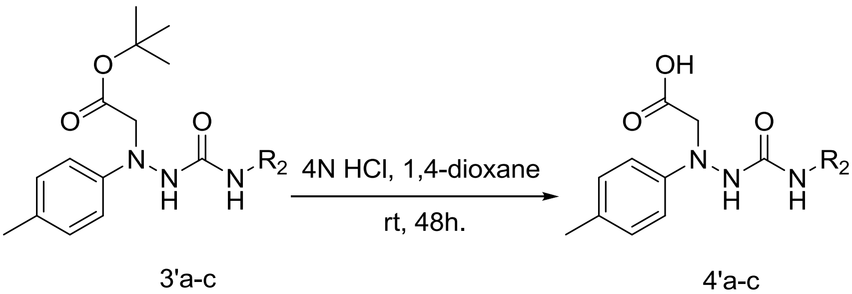


Compound 3'b: Yield: 70%; ^{1}H NMR (500 MHz, CDCl3) δ 7.9 (s, 1H), 7.25 (d, *J*=8.5 Hz, 2H), 7.22 (t, *J*=3 Hz, *J*=14.5 Hz, 1H), 7.18 (t, *J*=4.5 Hz, *J*=5.5 Hz, 2H), 7.01 (d, *J*=10.5 Hz, 2H), 6.63 (d, *J*=11 Hz, 2H), 3.32 (s, 3H), 1.38 (t, *J*=4.5 Hz, *J*=10 Hz, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 170.2, 170.2, 158.5, 146.9, 140.8, 129.8(2C), 128.6(2C), 127.2(2C), 126.9, 113(2C), 81.9, 57.9, 42.9, 28.2(3C), 20.4; LRMS (ESI) *m/z* calcd for $C_{21}H_{27}N_3O_3$ $[M+1]^+$: 370.21; Found: 370.05.



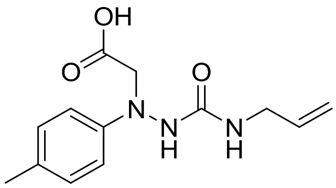
Compound 3’c: Yield: 59%; ^{1}H NMR (500 MHz, CDCl3) δ 8.61 (s, 1H), 7.42 (d, *J*=5, 2H), 7.30 (d, *J*=5, 2H), 7.13(d, *J*=5, 2H), 7.00(d, *J*=10), 3.96 (s, 2H), 2.31 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ 173.2, 172.8, 163.6, 156.6, 140.3, 130.6(2C), 116.4(2C), 116.1(2C), 113.4(2C), 112.2, 75.4, 65.4, 28.8, 20.8; LRMS (ESI) *m/z* calcd for $C_{20}H_{24}FN_3O_3$ $[M+1]^+$: 374.18; Found: 374.03.

3.2.3. General synthetic procedure for intermediate compounds 4’a-c

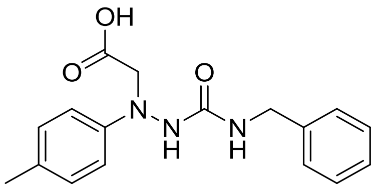


A 500 ml round-bottom-flash was fitted with a glass stopper and reflux condenser. A suspension of **3’a-c** (10g) in HCl (20ml, 4N solution in 1,4-Dioxane) was added to the flask and stirred at room temp for overnight until starting material were consumed. The reaction mixture was concentrated completely by rotary evaporation at 40^{0}C at aspirator vacuum. The saturated aq. $NaHCO_3$ solution was added (to pH 10) and the aqueous layer was washed with ethyl acetate (EA) (200ml X 3). Conc. HCl was added dropwise (to pH 2-3). The mixture was extracted with ethyl acetate (EA) (200ml X 3), and the organic layer was dried over Na_2SO_4 and evaporated.

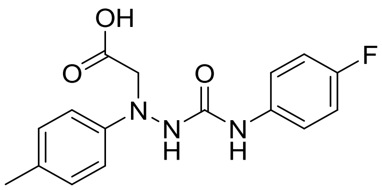
The residue was purified by crystallization with n-hexane and ethyl acetate to obtain **4’a-c**.



Compound 4’a: Yield: 78%; ^{1}H NMR (500 MHz, DMSO-d6) δ 12.55 (s, 1H), 8.01 (s, 1H), 7.02 (d, 2H, *J*=7.5 Hz), 6.61 (d, 2H, *J*=8 Hz), 5.75-5.80 (m, 1H), 5.06 (d, 1H, *J*=17 Hz), 4.98 (d, 1H, *J*=10.5 Hz), 4.15 (d, 2H, *J*=35.5 Hz), 3.66 (s, 2H), 3.41 (s, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 172.8, 158.7, 146.7, 136.6(2C), 129.8(2C), 114.9, 112.7, 56.3, 41.8, 20.4; LRMS (ESI) *m/z* calcd for $C_{13}H_{17}N_3O_3$ [M+1]+:264.13; Found: 264.08.

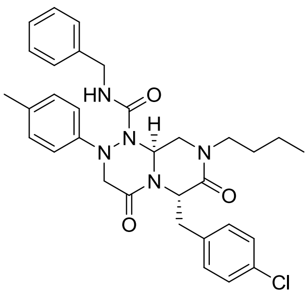


Compound 4’b: Yield: 80%; ^{1}H NMR (500 MHz, DMSO-d6) δ 12.55 (s, 1H), 8.02 (s, 1H), 7.38 (s, 1H), 7.27 (t, *J*=8 Hz, *J*=7 Hz, 3H), 7.21 (d, *J*=6.5 Hz, 2H), 7.19 (t, *J*=5.5 Hz, *J*=7.5 Hz, 2H), 7.02 (d, *J*=8.5 Hz, 2H), 6.63 (d, *J*=8.5 Hz, 2H), 4.24 (d, *J*=6 Hz, 2H), 3.34 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 172.7, 158.9, 146.8, 140.7, 129.8(2C), 128.6(2C), 128.1, 127.3(2C), 127.1 (2C), 112.8, 56.19, 43.1, 20.4; LRMS (ESI) *m/z* calcd for $C_{17}H_{19}N_3O_3$ $[M+1]^+$: 314.14; Found: 314.00.

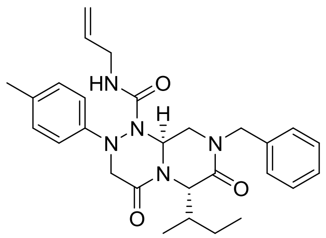


Compound 4'c: Yield: 75%; ^{1}H NMR (500 MHz, DMSO-d6) δ 12.85 (s, 1H), 9.27 (s, H), 8.42 (s, 1H), 7.48 (d, *J*=5 Hz, 2H), 7.09 (d, *J*=10 Hz, 2H), 7.05 (d, *J*=10 Hz, 2H), 6.70 (d, *J*=10 Hz, 2H), 4.09 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 173.2, 172.8, 130.6, 129.3, 121.0, 119.7, 116.4(2C), 116.3(2C), 116.2, 115.1(2C), 114.9(2C), 113.7, 54.0, 20.8; LRMS (ESI) *m/z* calcd for $C_{16}H_{16}N_3O_3$ $[M+1]^+$:318.12; Found: 317.93.

3.2.4. Spectroscopic Data for representative compounds



Compound 10{a,2,9}: ^{1}H NMR (500 MHz, CDCl3) δ 7.23-7.36 (m, 9H), 7.12 (d, *J*=8 Hz, 2H), 6.84 (d, *J*=8.5 Hz, 2H), 6.65 (dd, *J*=4 Hz, *J*=7.5 Hz, *J*=4 Hz, 1H), 6.60 (t, *J*=6 Hz, *J*=6 Hz, 1H), 5.17 (t, *J*=4 Hz, *J*=6 Hz, 1H), 4.54 (m, 2H), 4.22 (d, *J*=17 Hz, 1H), 3.90 (d, *J*=17.5 Hz , 1H), 3.76 (dd, *J*=13.5 Hz, J=5 Hz, *J*=13 Hz, 2H), 3.34 (m, 1H), 3.16 (m, 4H), 3.05 (m, 1H), 2.31 (s, 3H), 1.27 (m, 2H), 1.20 (m, 2H), 0.86 (t, *J*=7.5 Hz, *J*=7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 164.9, 162.9, 156.2, 132.8, 131.1, 130.9, 129.8, 129.4(2C), 129.1(2C), 129.1(2C), 128.6(2C), 128.2(2C), 128.0, 127.9, 127.6, 127.0, 126.4, 116.0, 114.7(2C), 62.2, 54.3, 54.1, 50.0, 47.0, 26.9, 13.8; LRMS (ESI) *m/z* calcd for $C_{32}H_{36}ClN_5O_3$ $[M+1]^+$: 574.25; Found: 574.22.



Compound 10{b,3,4}: ^{1}H NMR (500 MHz, CDCl3) δ 7.27 (m, 5H), 7.09 (t, *J*=3.5 Hz, *J*=4 Hz, 1H), 7.05 (d, *J*=8.5 Hz, 2H), 6.75 (d, *J*=8.5 Hz, 2H), 6.38 (dd, *J*=6.5 Hz, *J*=2 Hz, *J*=6.5 Hz, 1H), 6.13 (t, *J*=6 Hz, *J*=6 Hz, 1H), 5.83 (m, 1H), 5.14 (dd, *J*=7 Hz, *J*=5 Hz, *J*=5 Hz, 2H), 4.67 (d, *J*=15 Hz,1H), 4.49 (s, 1H), 4.28 (d, *J*=17 Hz, 1H), 4.20 (d, *J*=14.5 Hz, 1H), 4.02 (d, *J*=17 Hz, 1H), 3.95 (m, 1H), 3.87 (m, 1H), 3.065 (t, *J*=6.5 Hz, *J*=2 Hz, 2H), 2.9 (s, 3H), 2.23 (m, 1H), 1.61 (m, 2H), 1.39 (m, 2H), 1.11 (d, *J*=7 Hz, 3H), 0.97 (t, *J*=7.5 Hz, *J*=7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 162.6, 161.7, 156.5, 152.8, 143.7, 135.7, 131.1(2C), 129.3, 128.7(2C), 128.2(2C), 127.4, 114.5(2C), 113.5, 85.2 60.6, 59.9, 59.1, 50.5, 48.6, 42.3, 38.7, 26.5, 15.8, 10.1; LRMS (ESI) *m/z* calcd for $C_{28}H_{35}N_5O_3$ $[M+1]^+$: 490.27; Found: 490.09.

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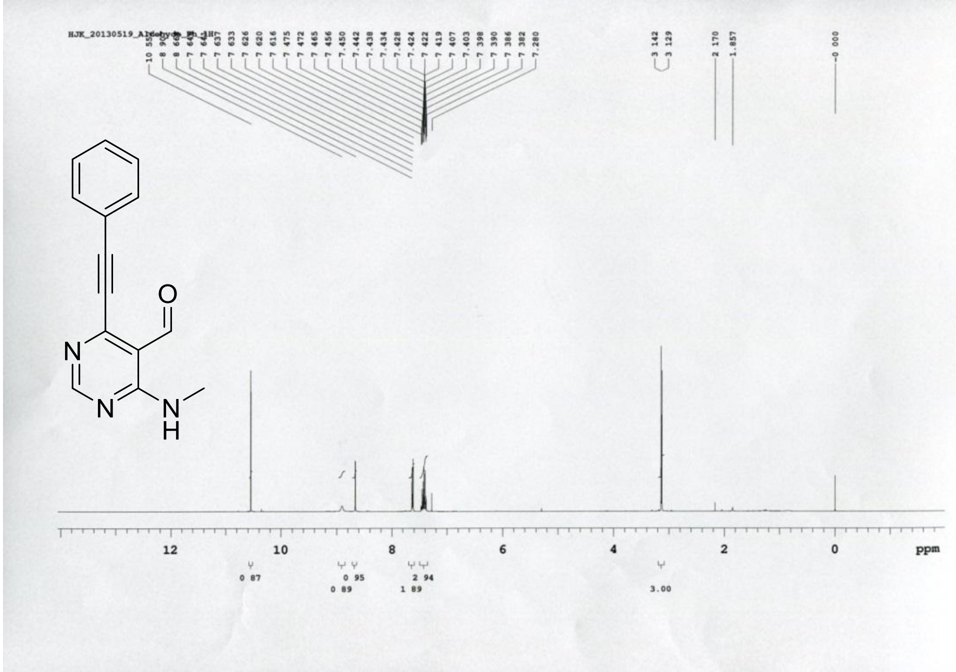
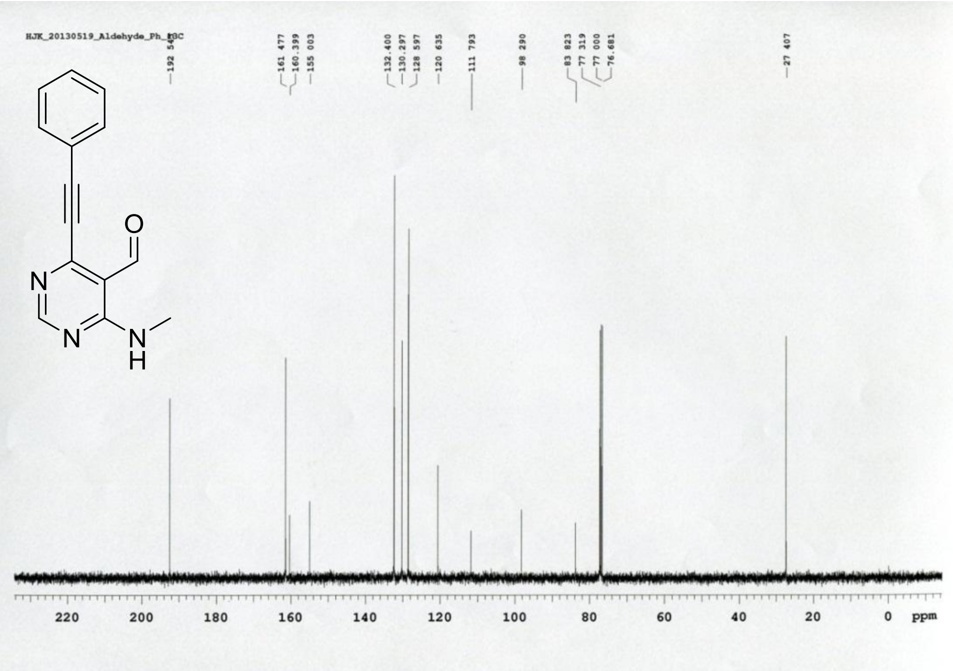
SUPPORTING INFORMATION

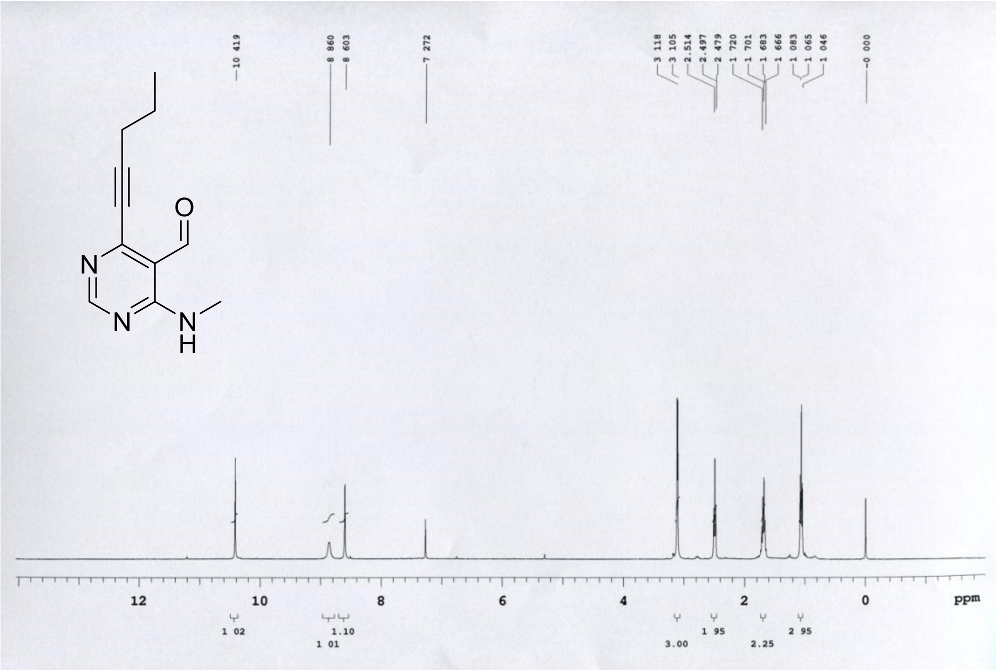
CHAPTER 1

Compound 1a





Compound 1b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1 065
1 046
0 000
N
N
O
N
H
12
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8
6
4
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0
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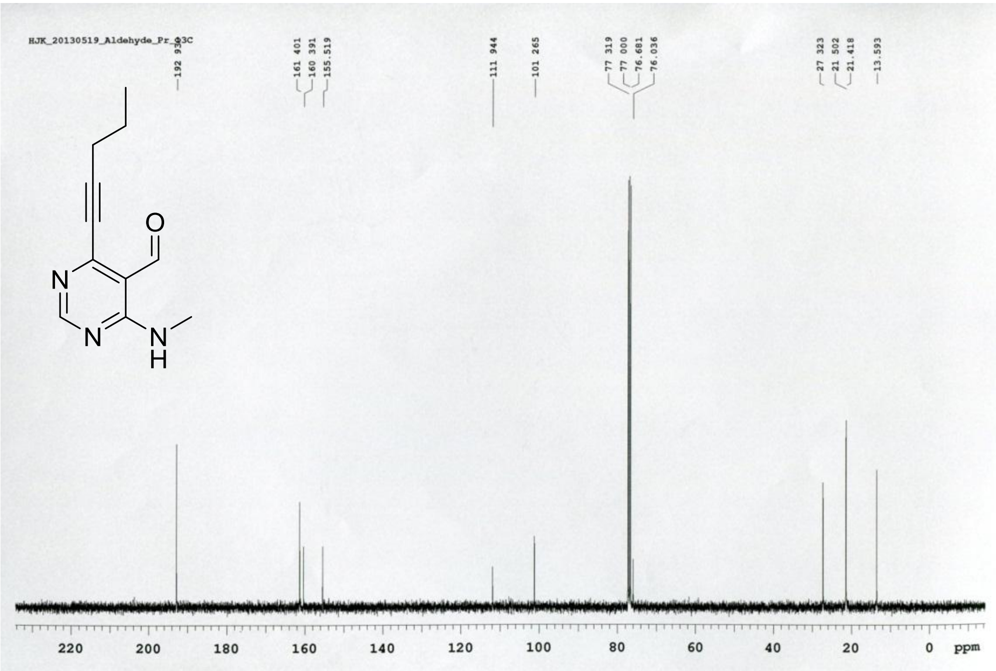
1 01
3.00
1 95
2.25
2 95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H
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60
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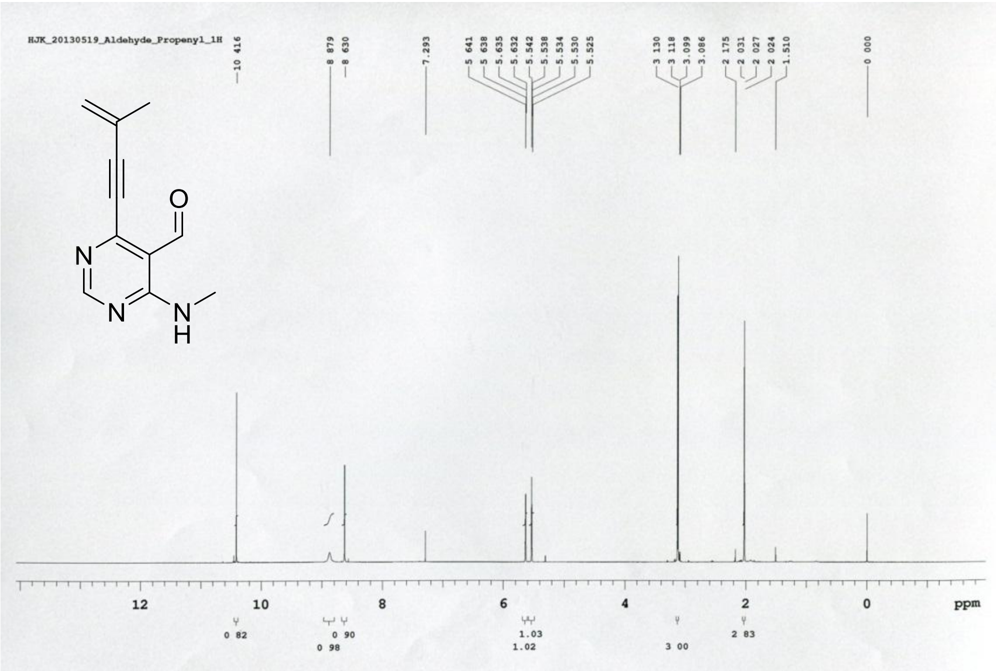
ppm

Compound 1c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3 118
3.099
3.086
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2 031
2 027
2 024
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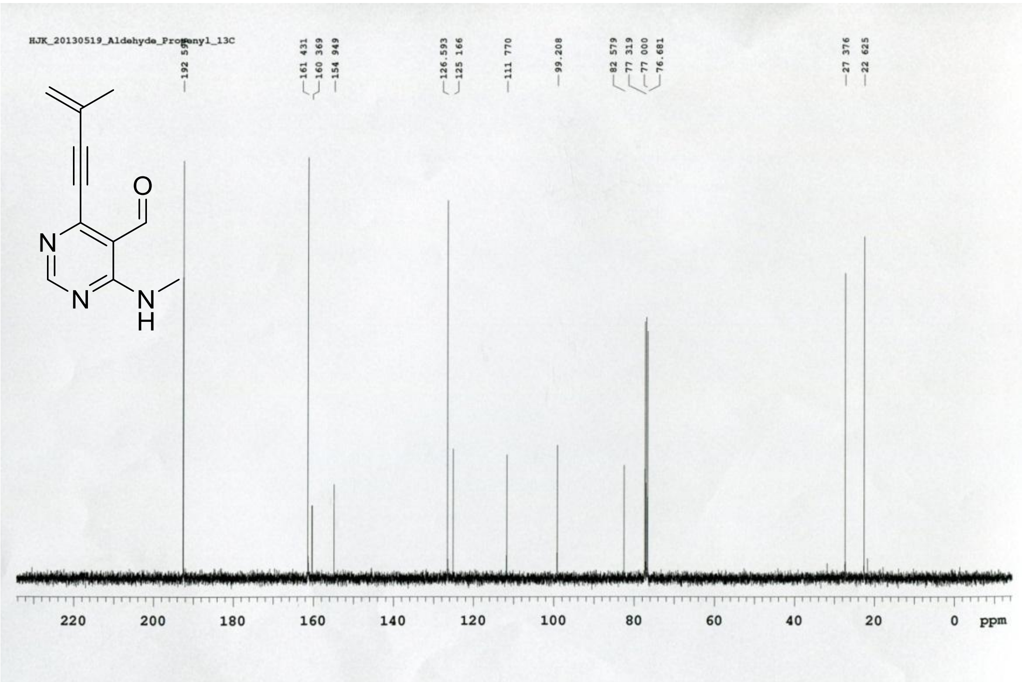
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180
160
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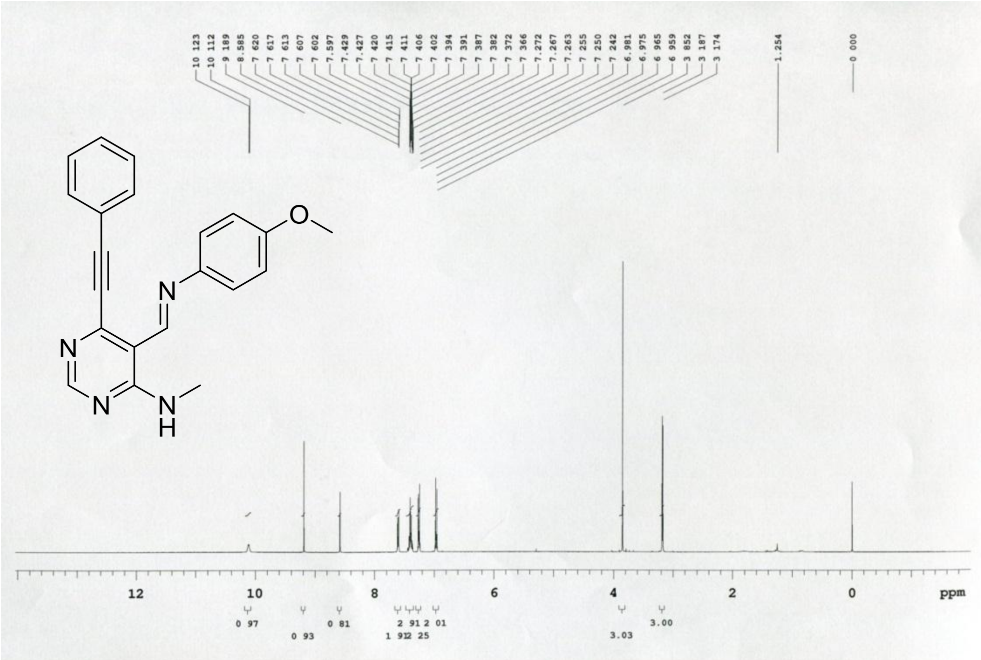
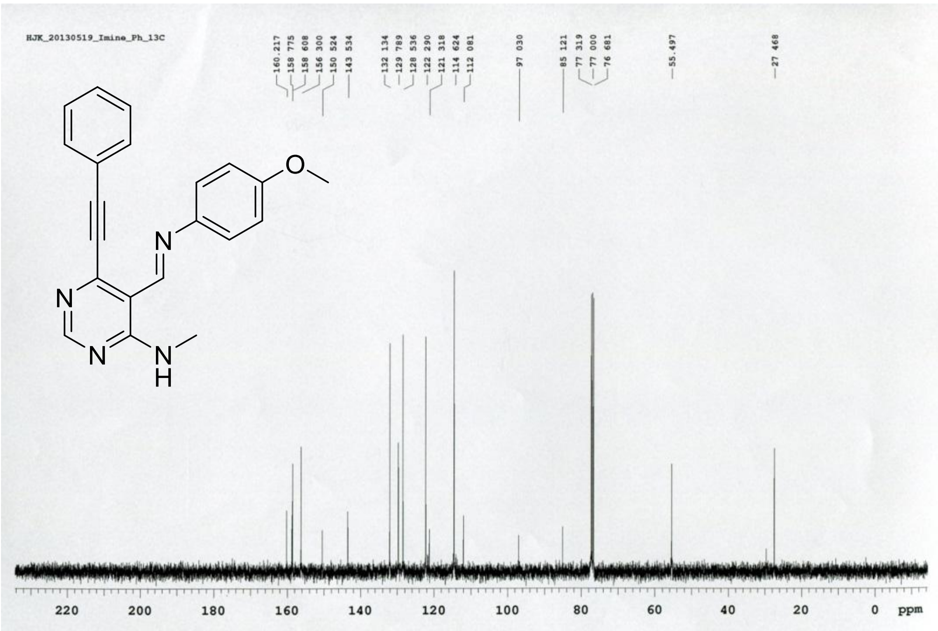
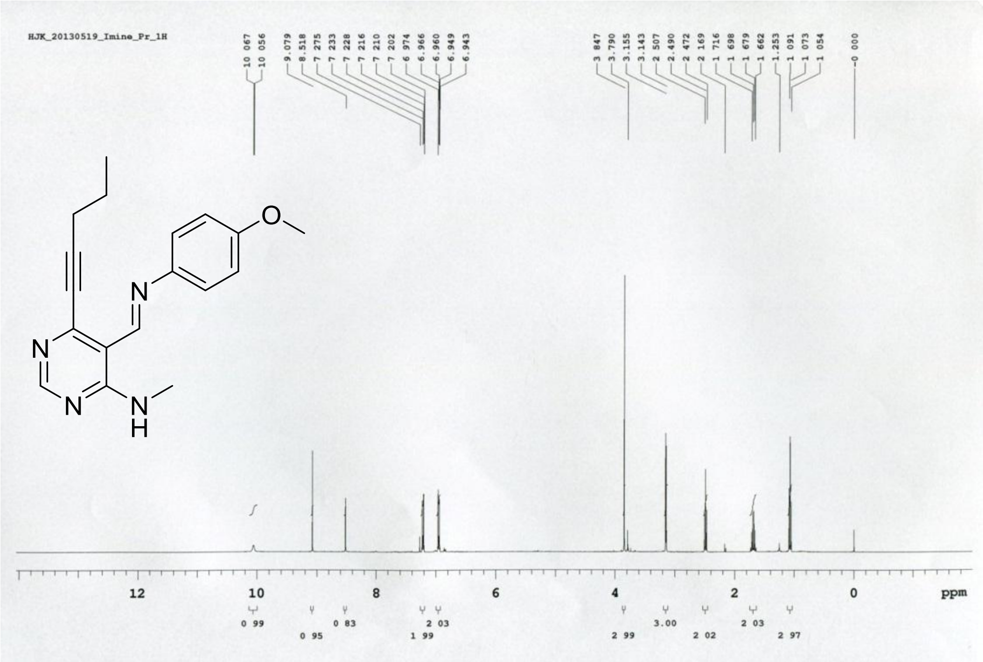
120
100
80
60
40
20
0
ppm

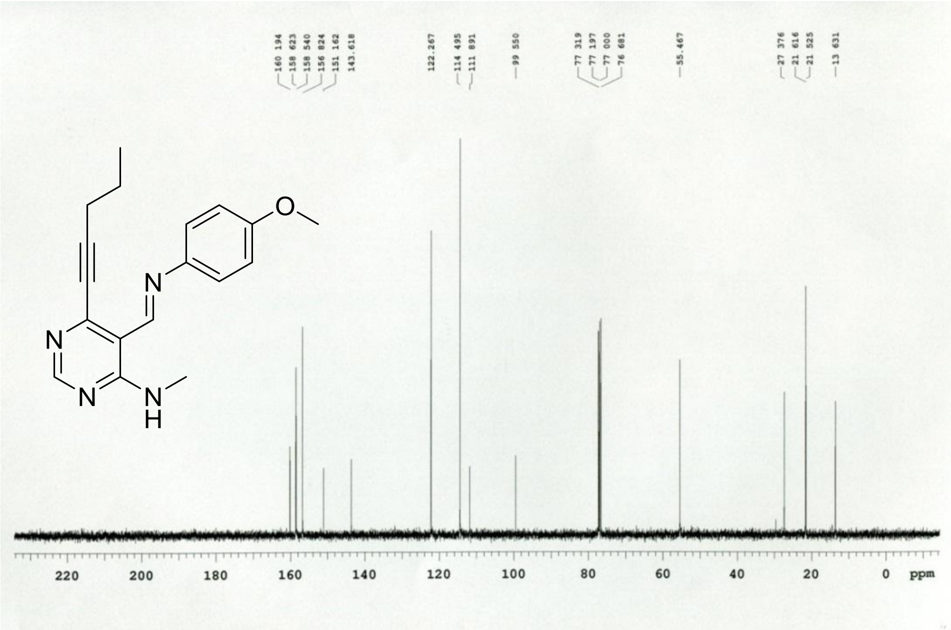
Compound 1d



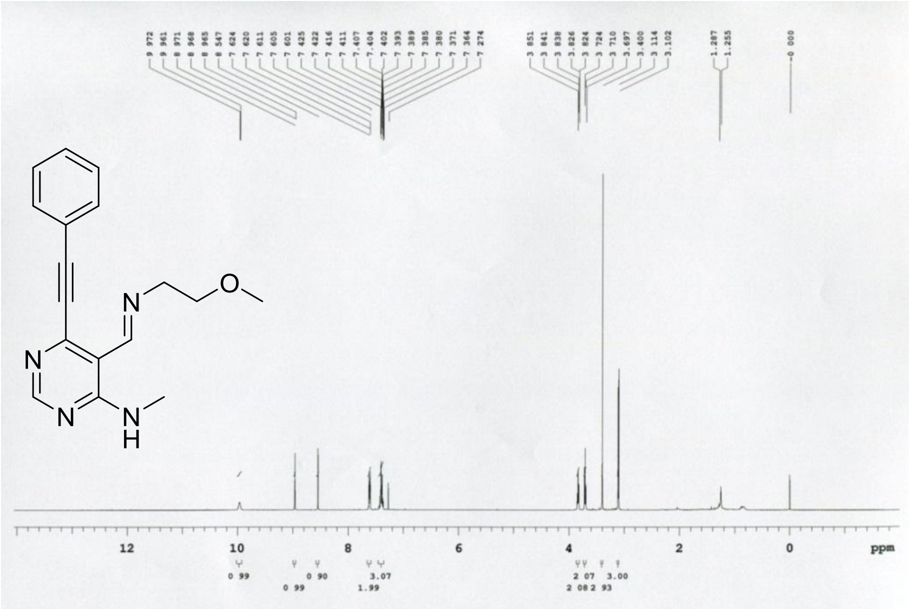


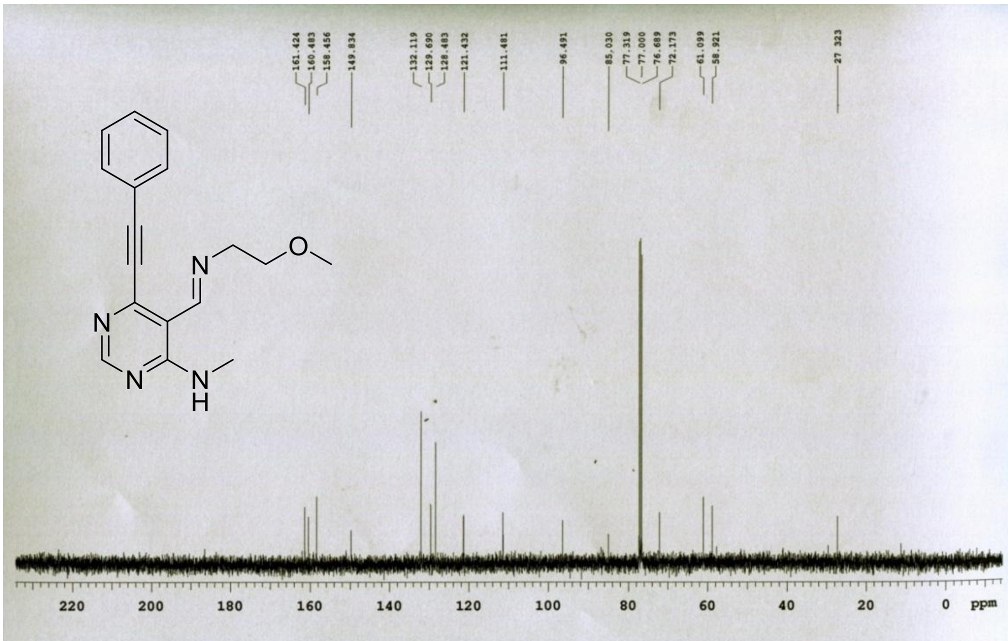
Compound 1e



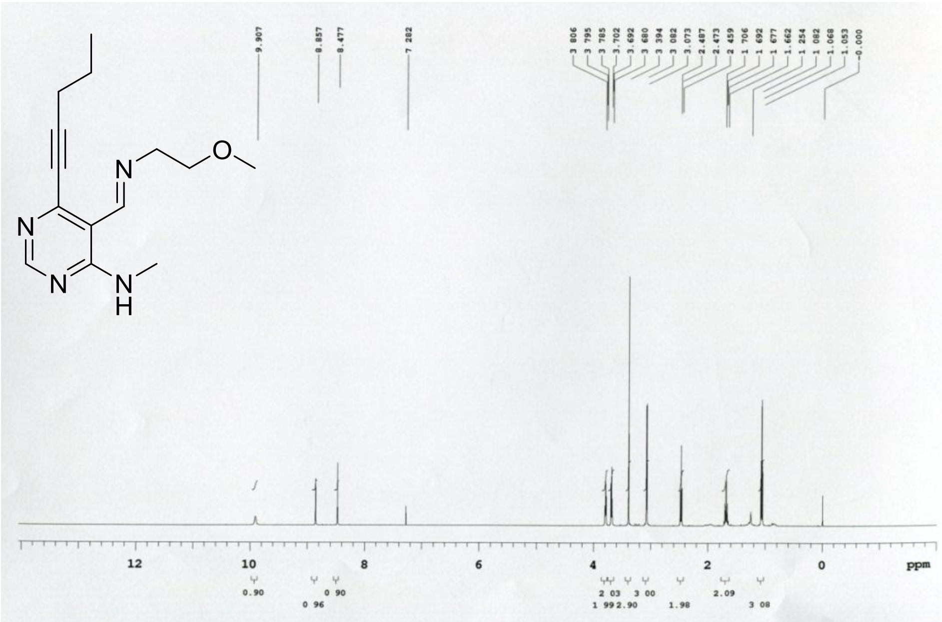


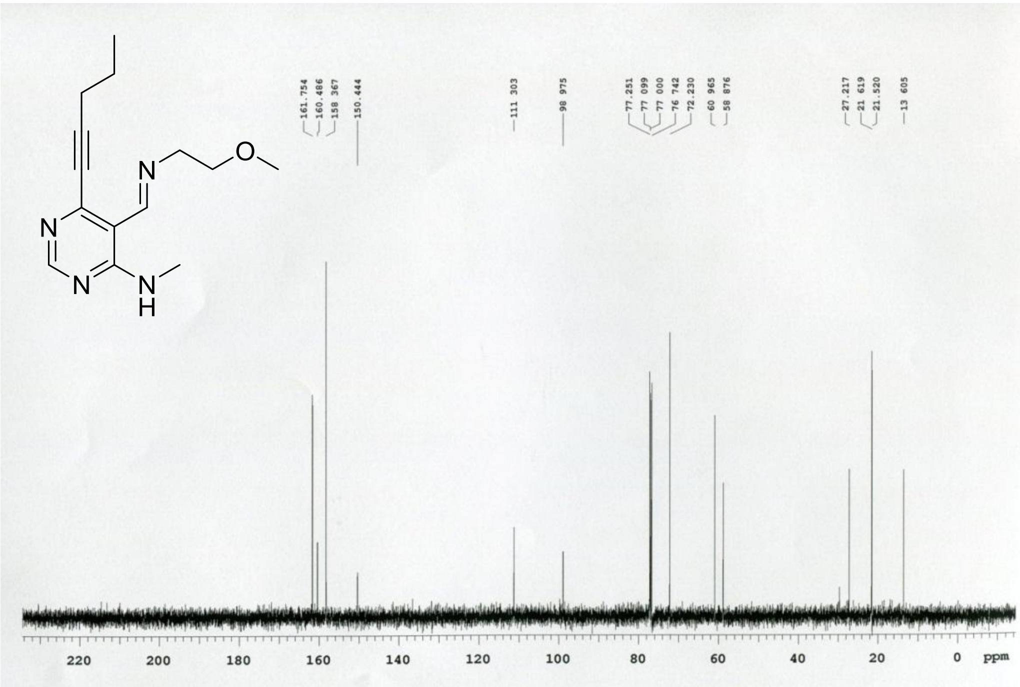
Compound 1f



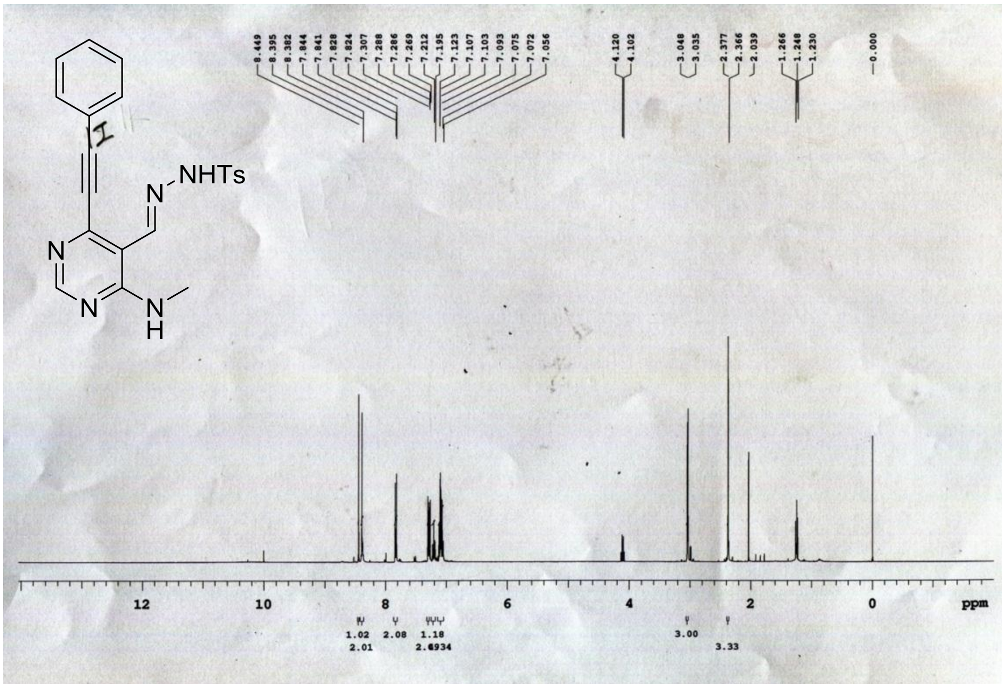


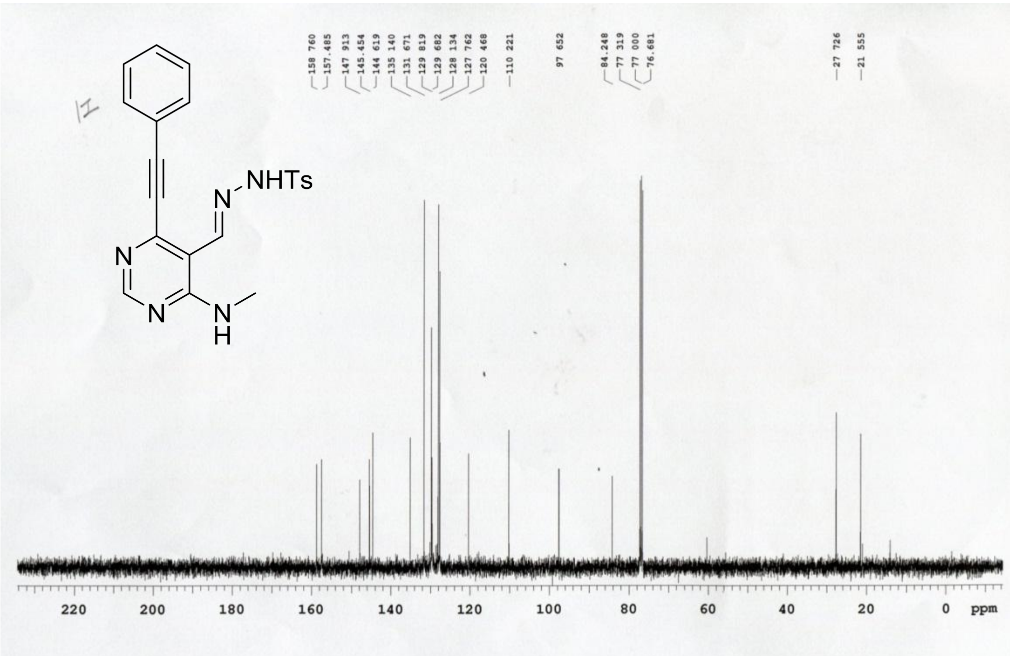
Compound 1g



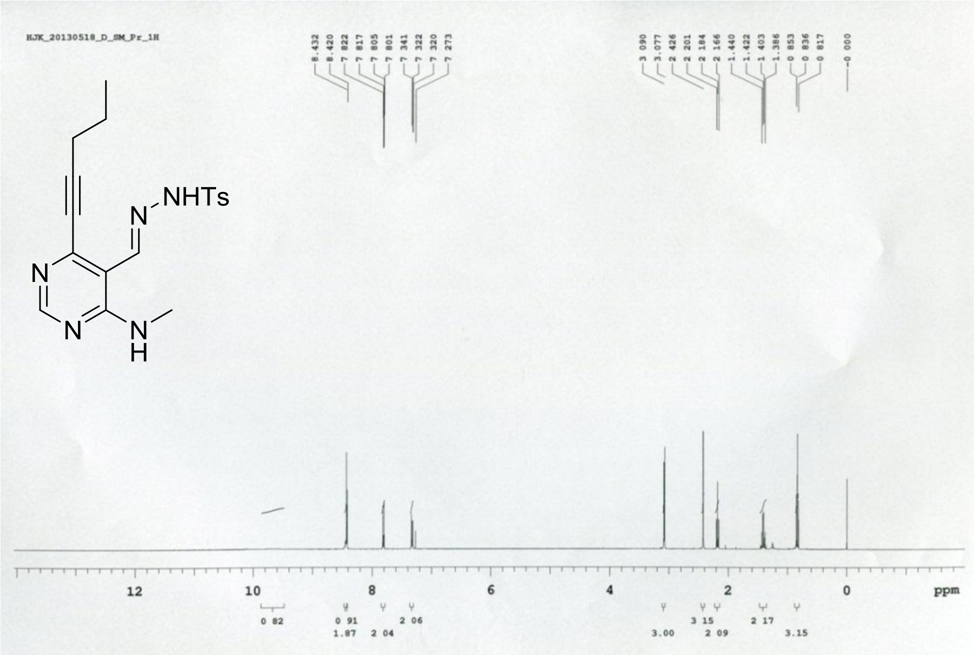


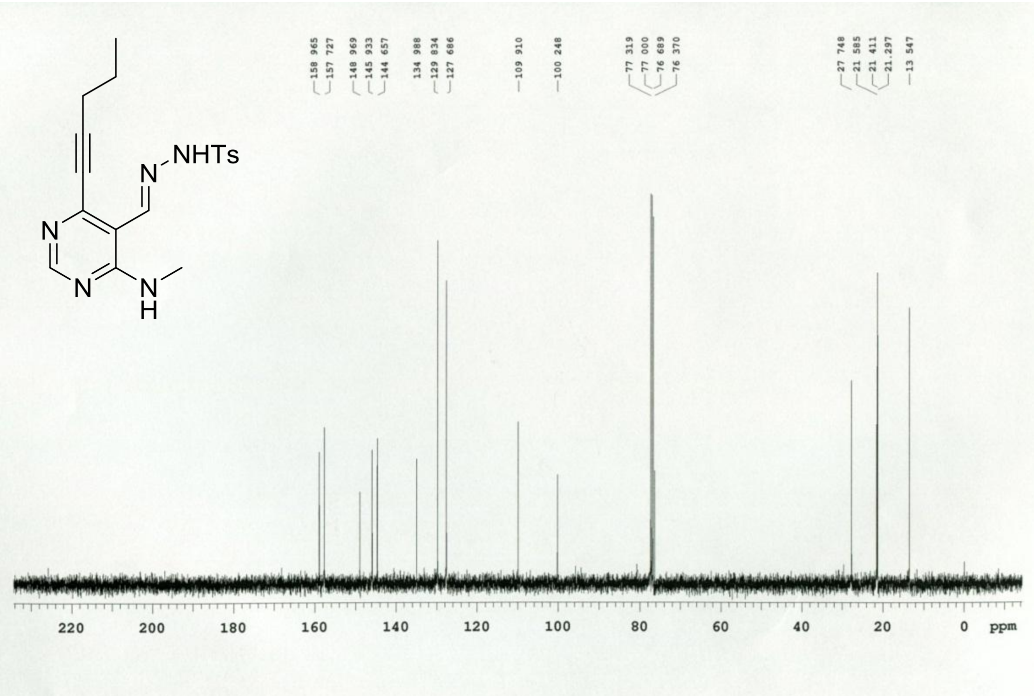
Compound 1h


NHTs
N
N
N
N
H
8.449
8.395
8.382
7.844
7.841
7.828
7.824
7.307
7.288
7.286
7.269
7.212
7.195
7.123
7.107
7.103
7.093
7.075
7.072
7.056
4.120
4.102
3.048
3.035
2.377
2.366
2.039
1.266
1.248
1.230
0.000
12
10
8
6
4
2
0
ppm
1.02
2.01
2.08
1.18
3.00
3.33

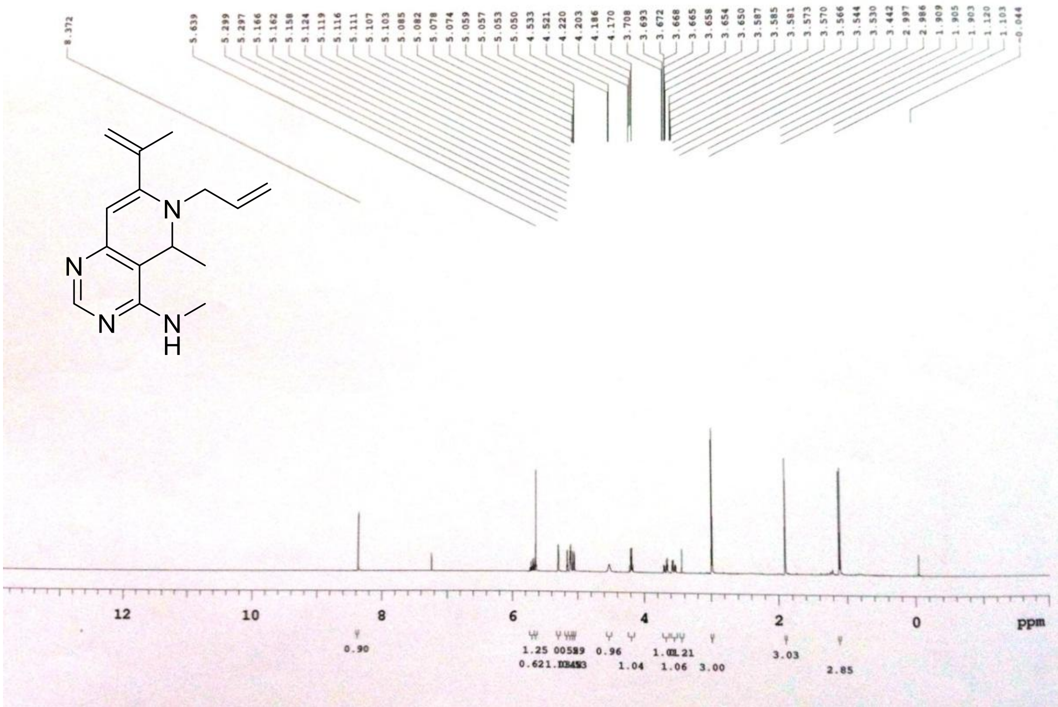

NHTs
N
N
N
N
H
158.760
157.485
147.913
145.454
144.619
135.140
131.671
129.819
129.682
128.134
127.762
120.468
110.221
97.652
84.248
77.319
77.000
76.681
27.726
21.555
220
200
180
160
140
120
100
80
60
40
20
0
ppm

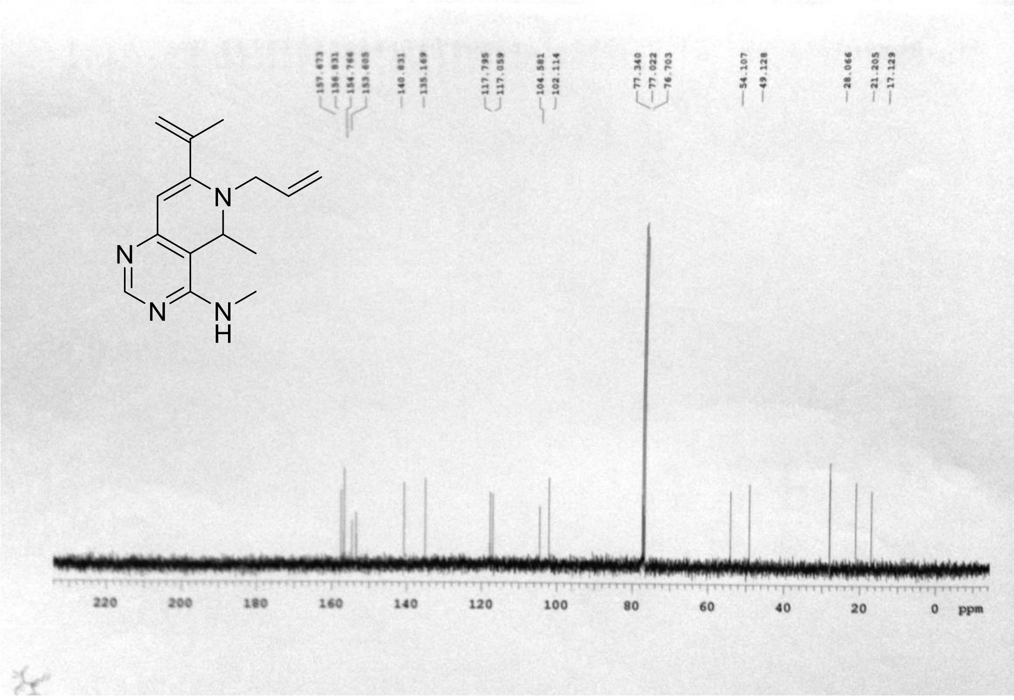
Compound 1i



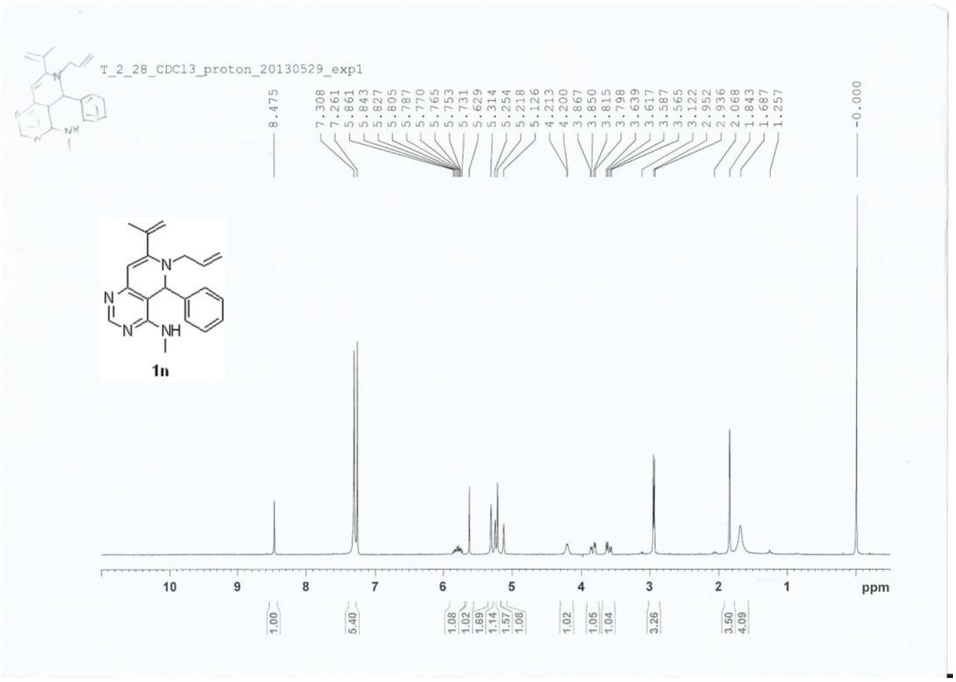


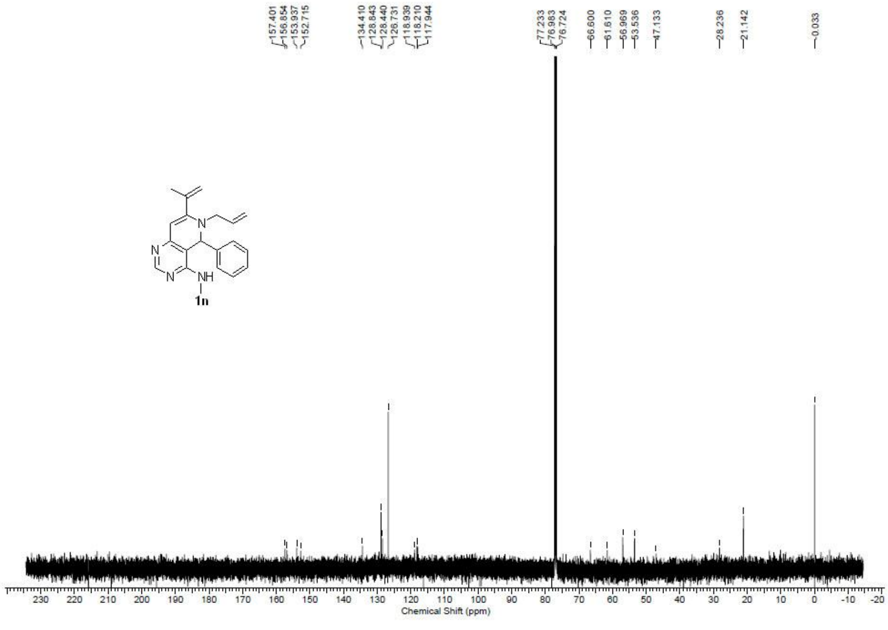
Compound 1j



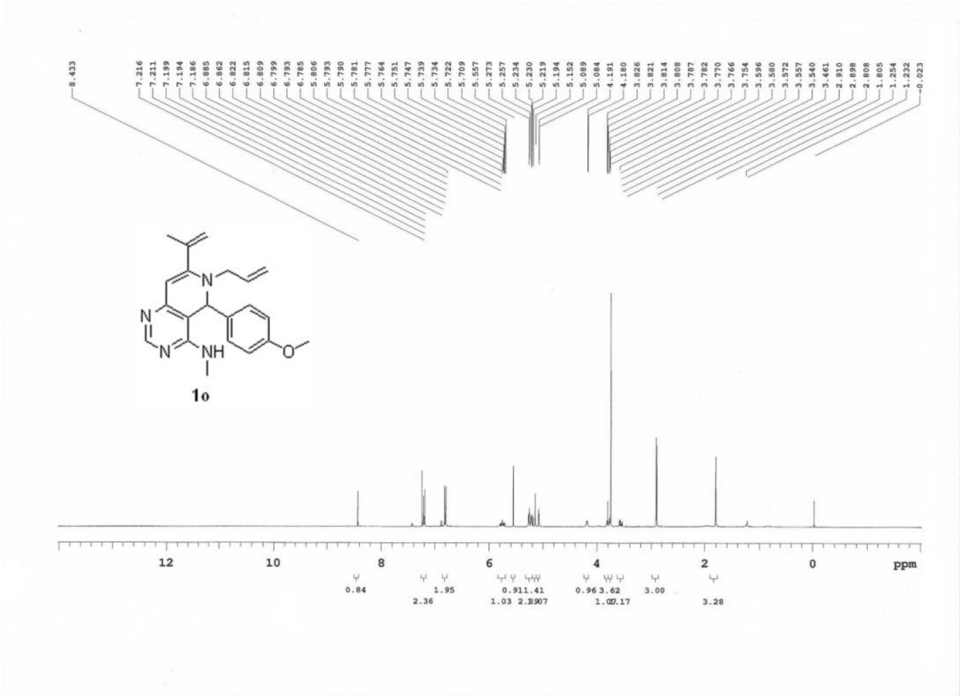


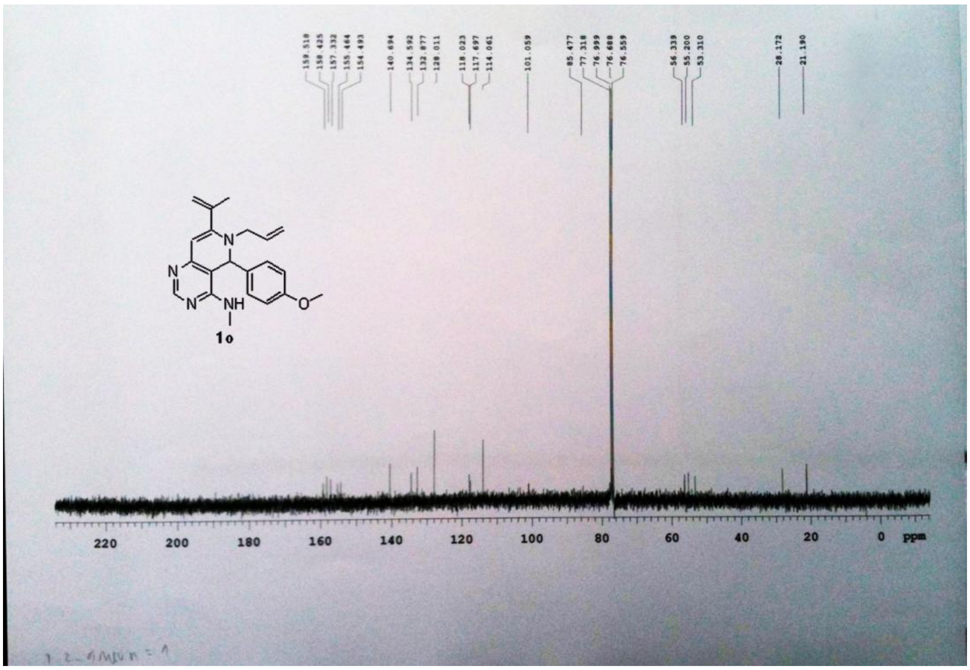
Compound 1k



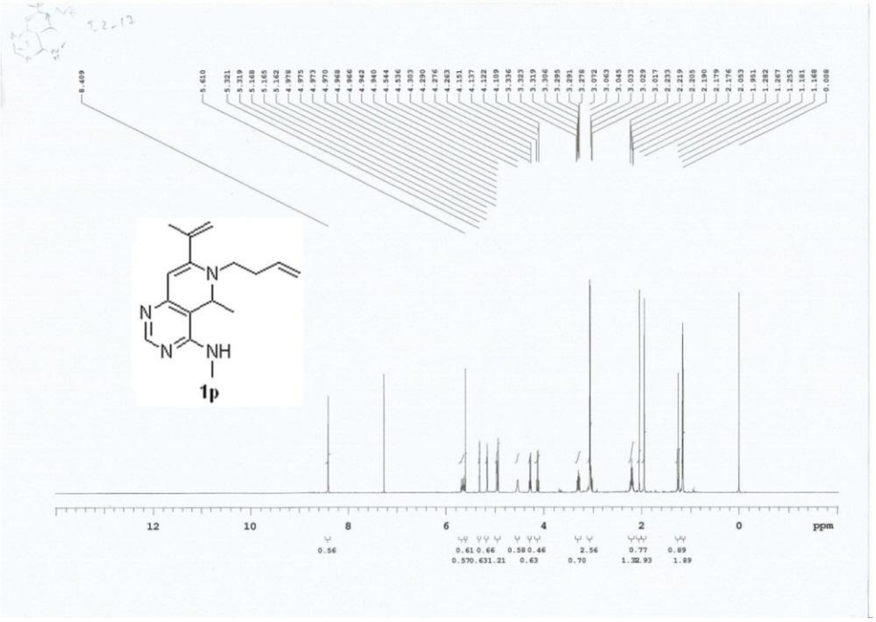


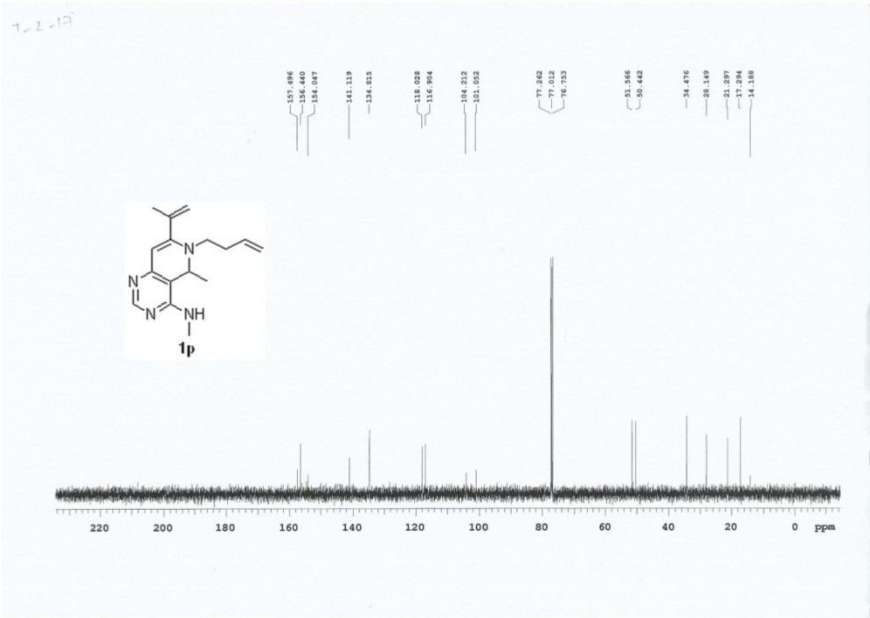
Compound 1l



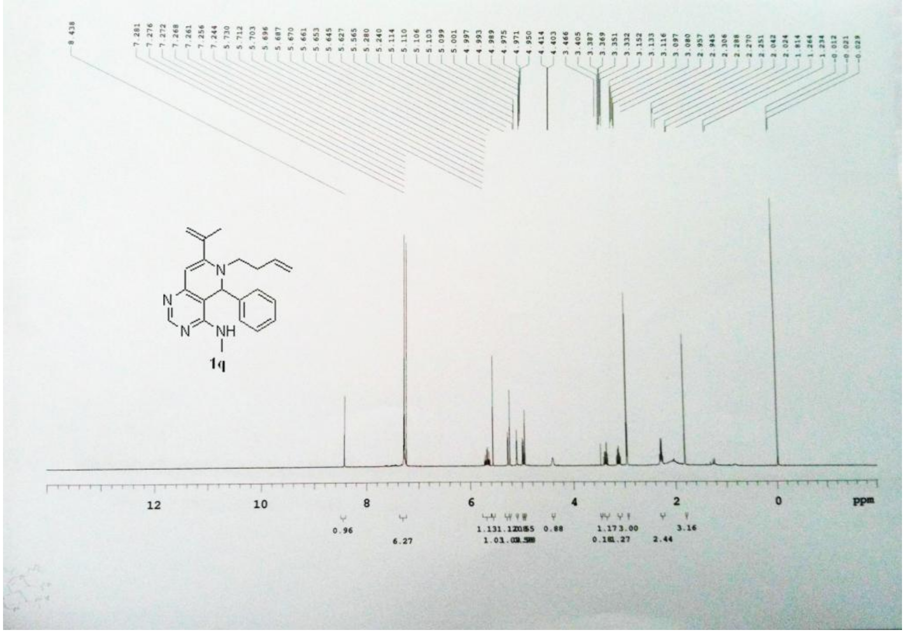


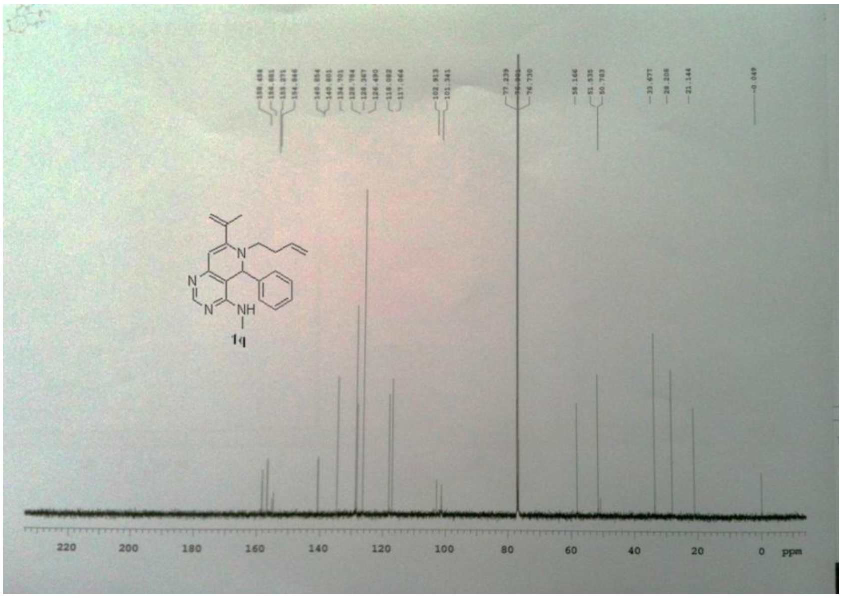
Compound 1m



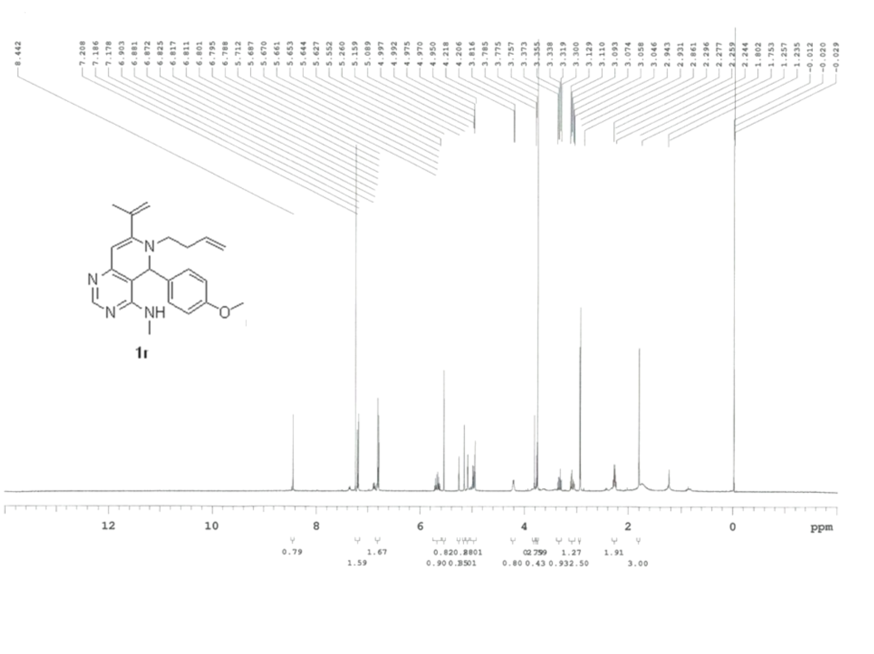


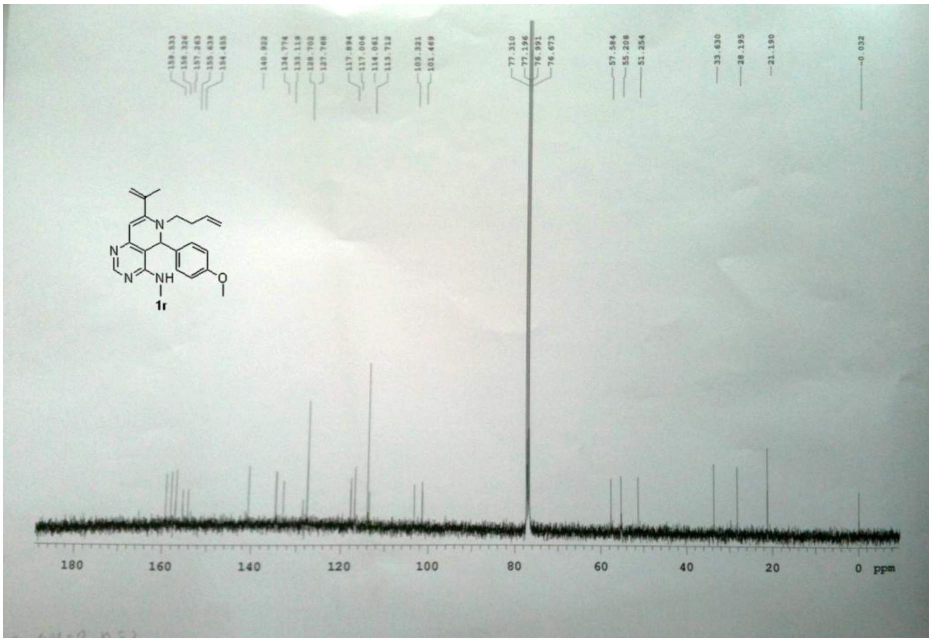
Compound 1n



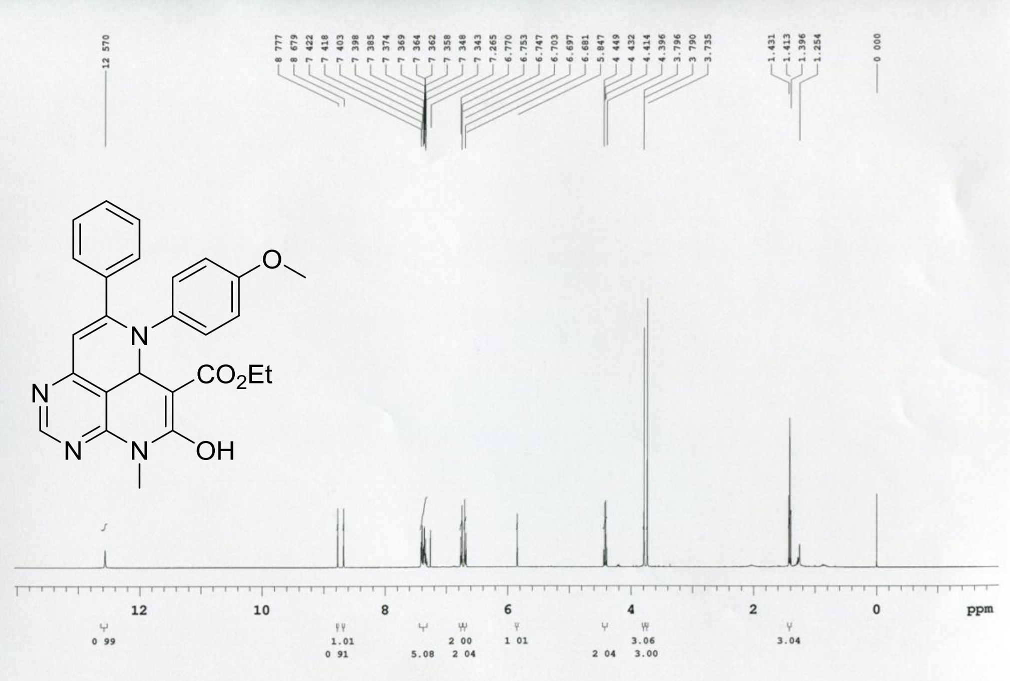


Compound 1o

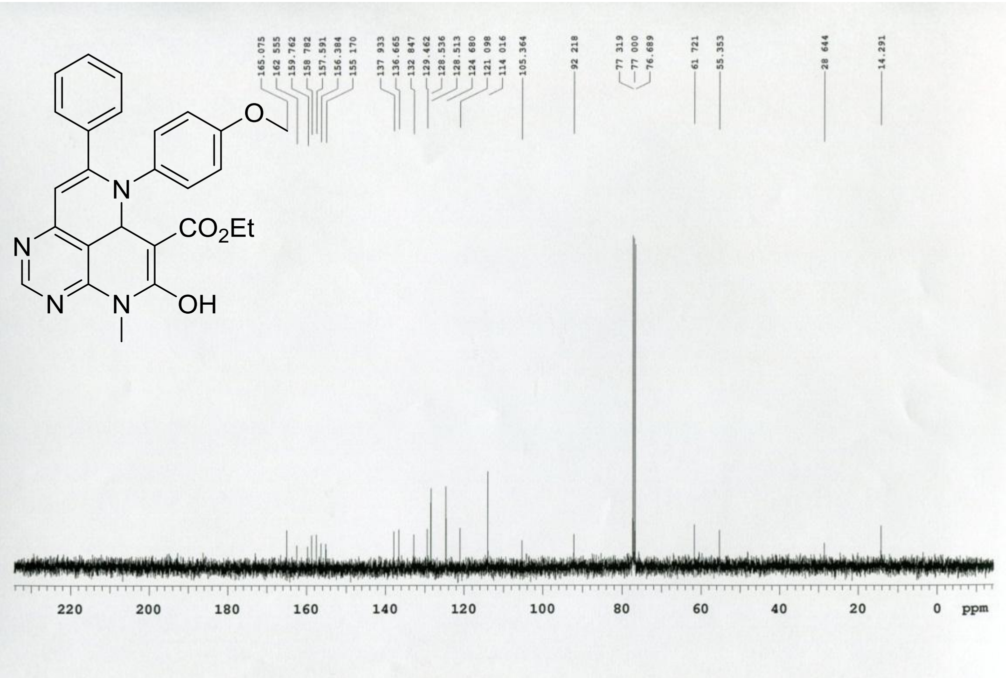




Compound 2a

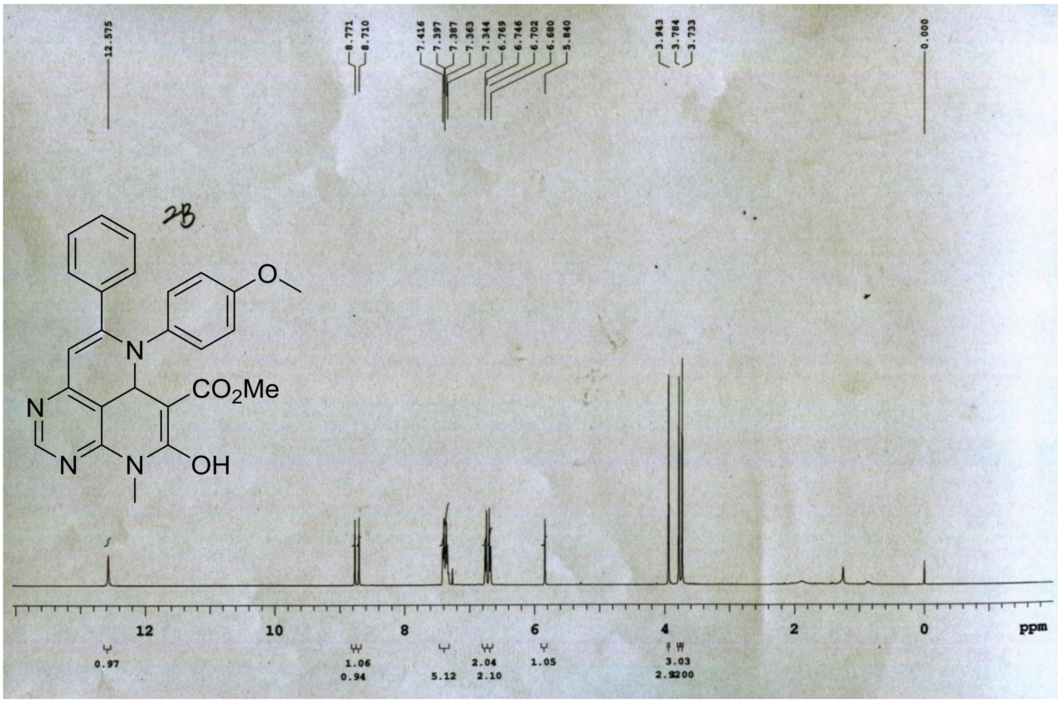


12.570
8.777
8.679
7.422
7.418
7.403
7.398
7.385
7.374
7.369
7.364
7.362
7.358
7.348
7.343
7.265
6.770
6.753
6.747
6.703
6.697
6.681
5.847
4.449
4.432
4.414
4.396
3.796
3.790
3.735
1.431
1.413
1.396
1.254
0.000
N
N
N
N
O
CO2Et
OH
ppm
0.99
1.01
0.91
5.08
2.00
2.04
1.01
2.04
3.06
3.00
3.04

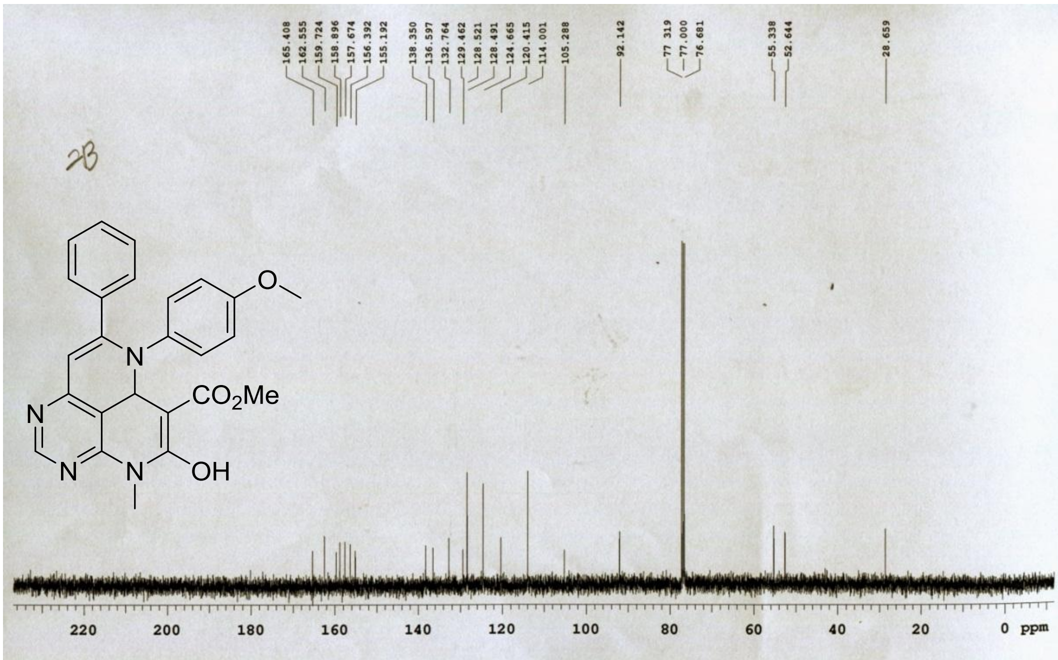


165.075
162.555
159.762
158.782
157.591
156.384
155.170
137.933
136.665
132.847
129.462
128.536
128.513
124.680
121.098
114.016
105.364
92.218
77.319
77.000
76.689
61.721
55.353
28.644
14.291
N
N
N
N
O
CO2Et
OH
ppm

Compound 2b

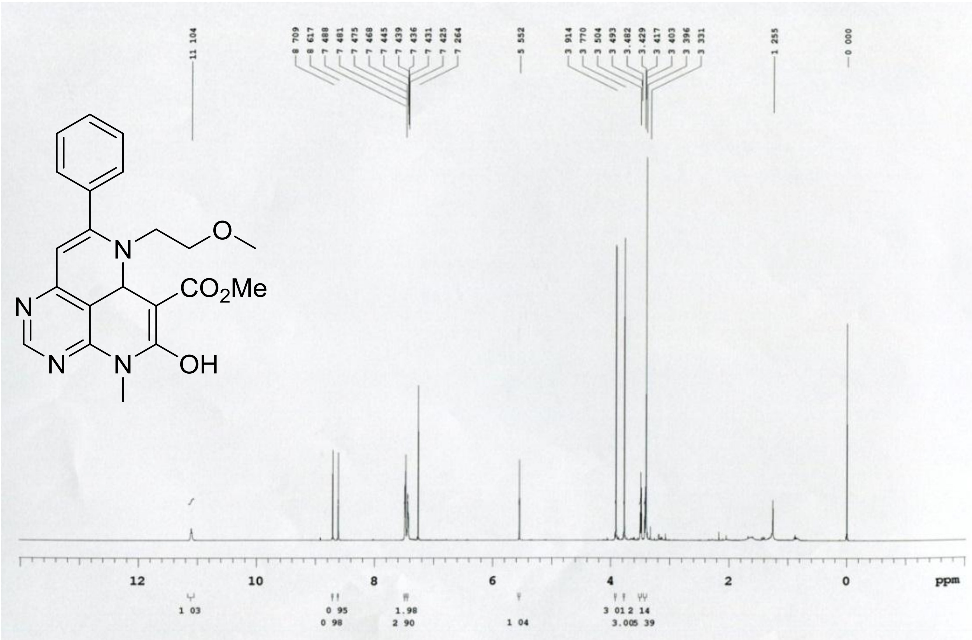


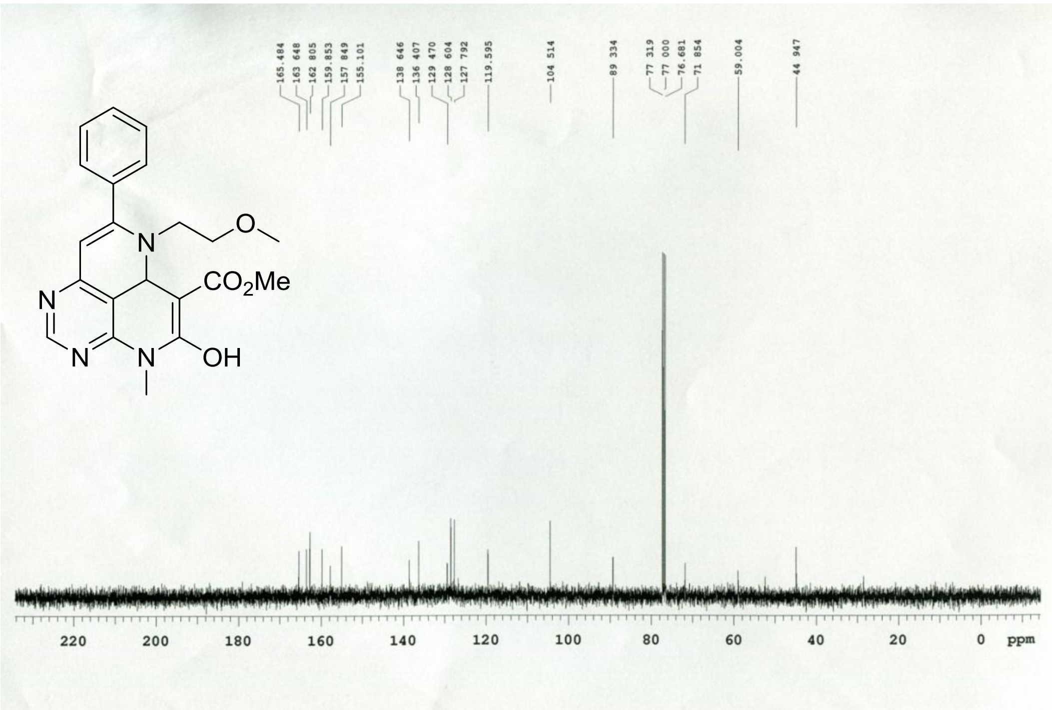
12.575
8.771
8.710
7.416
7.397
7.387
7.363
7.344
6.769
6.746
6.702
6.680
5.840
3.943
3.784
3.733
0.000
2B
O
N
CO_2Me
N
N
N
OH
12
10
8
6
4
2
0
ppm
0.97
1.06
0.94
5.12
2.04
2.10
1.05
3.03
2.92
00



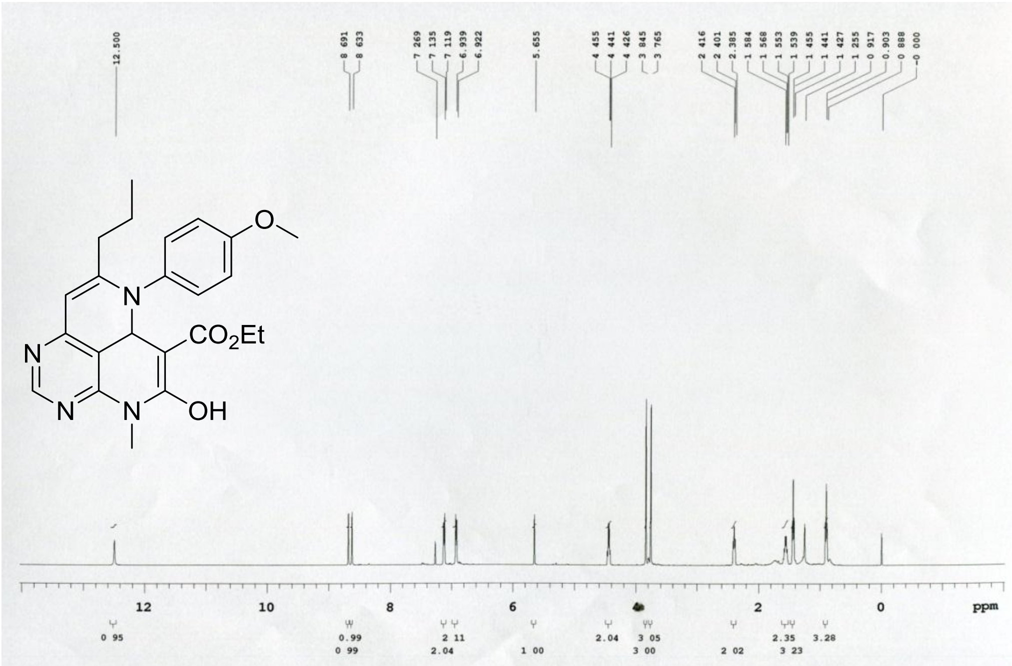
165.408
162.555
159.724
158.896
157.674
156.392
155.192
138.350
136.597
132.764
129.462
128.521
128.491
124.665
120.415
114.001
105.288
92.142
77.319
77.000
76.681
55.338
52.644
28.659
2B
O
N
CO_2Me
N
N
N
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

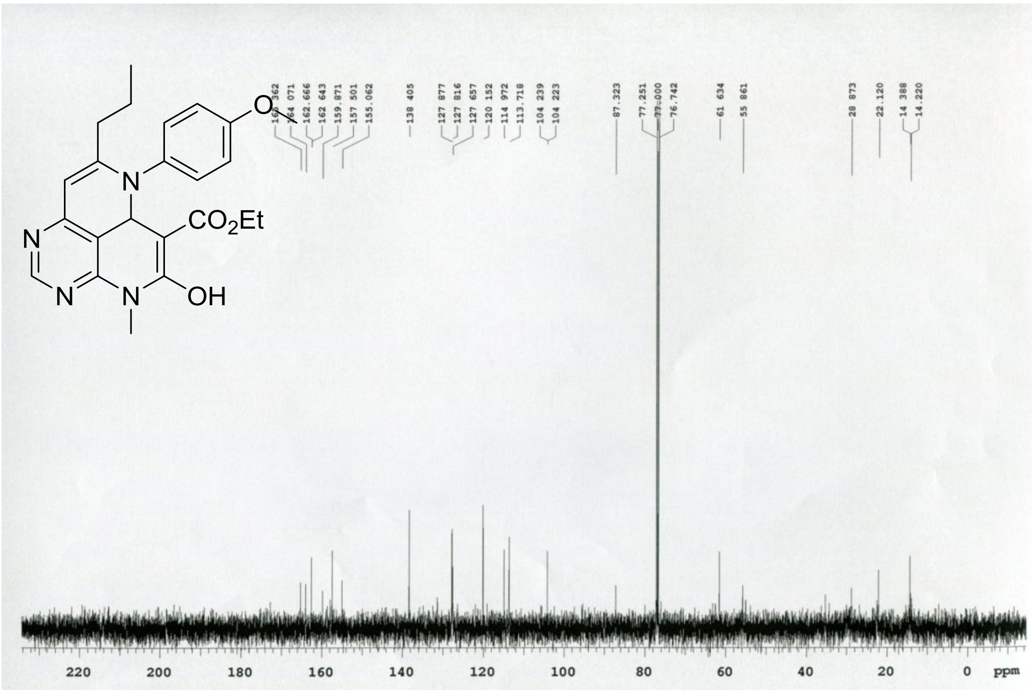
Compound 2c



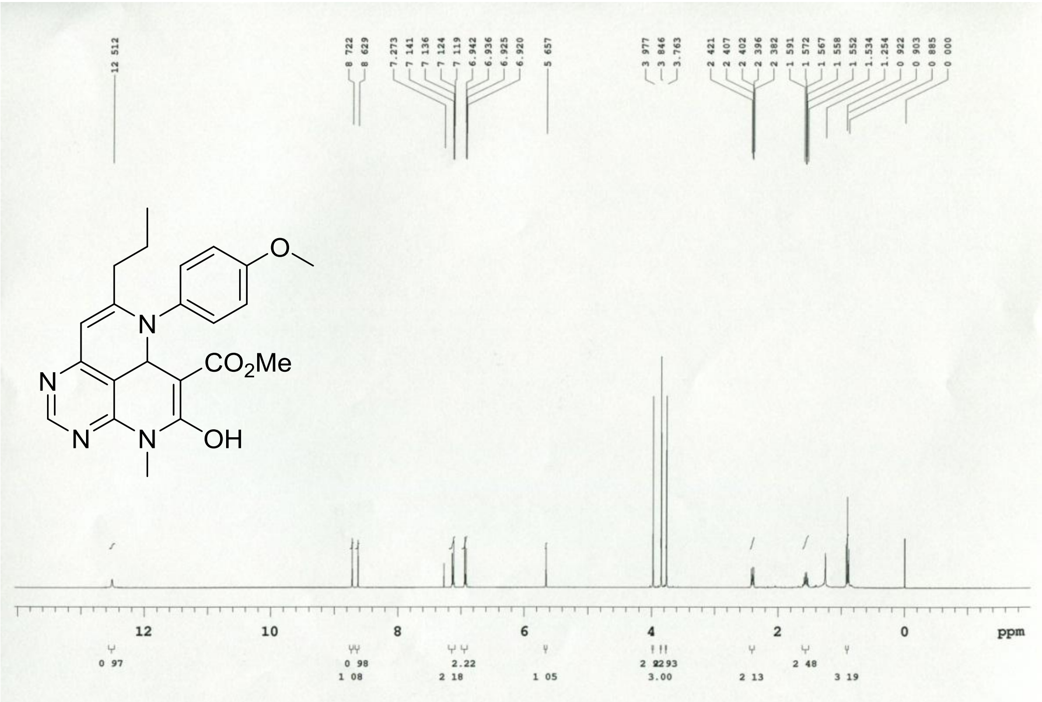


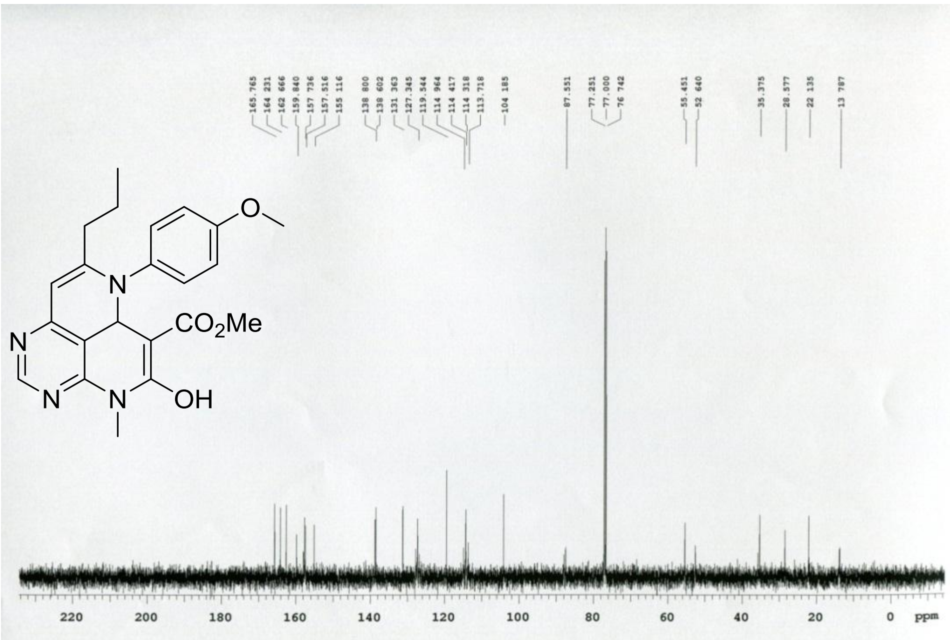
Compound 2d



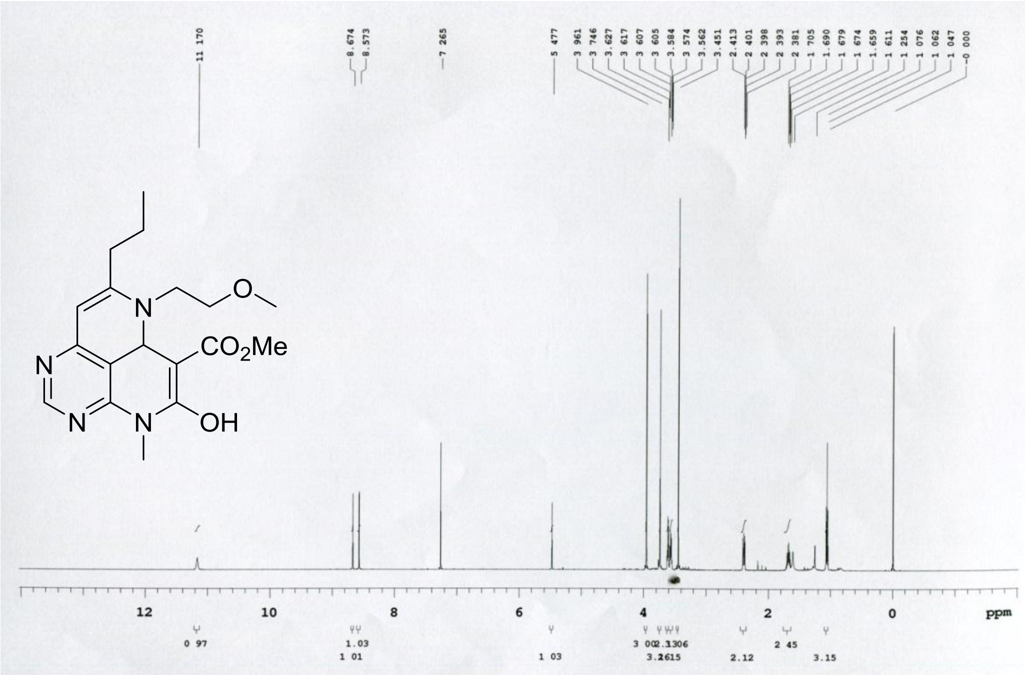


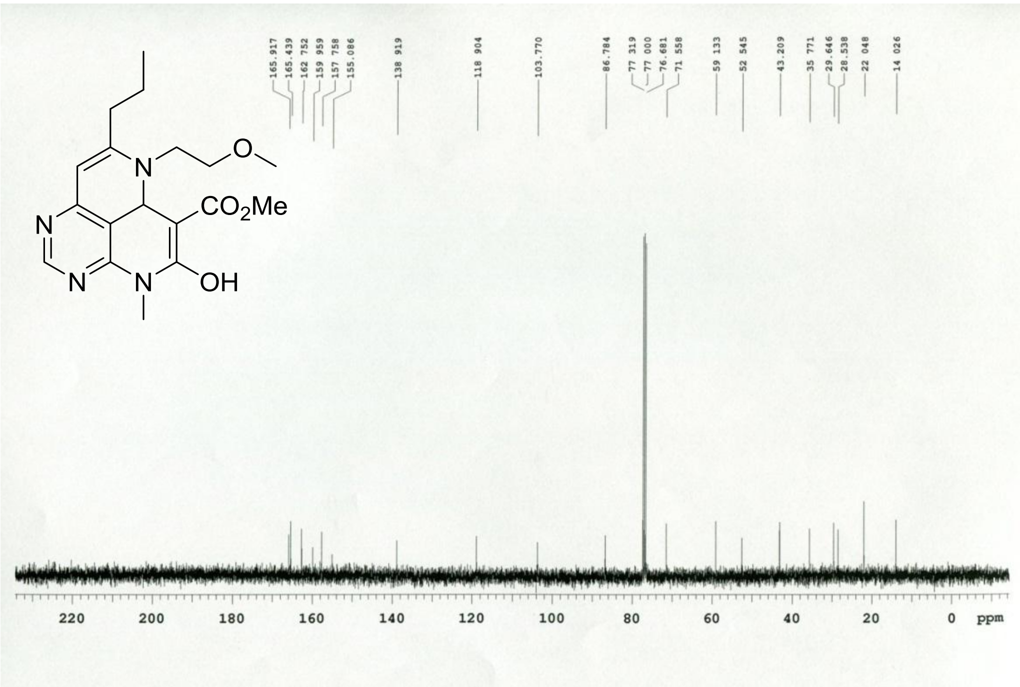
Compound 2e



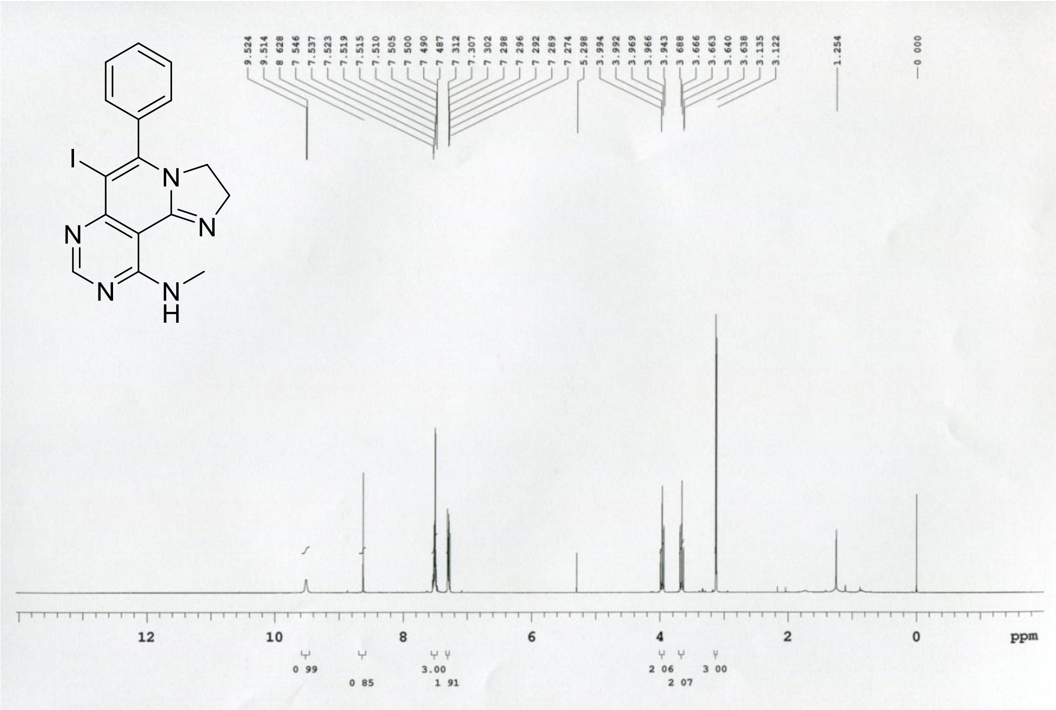


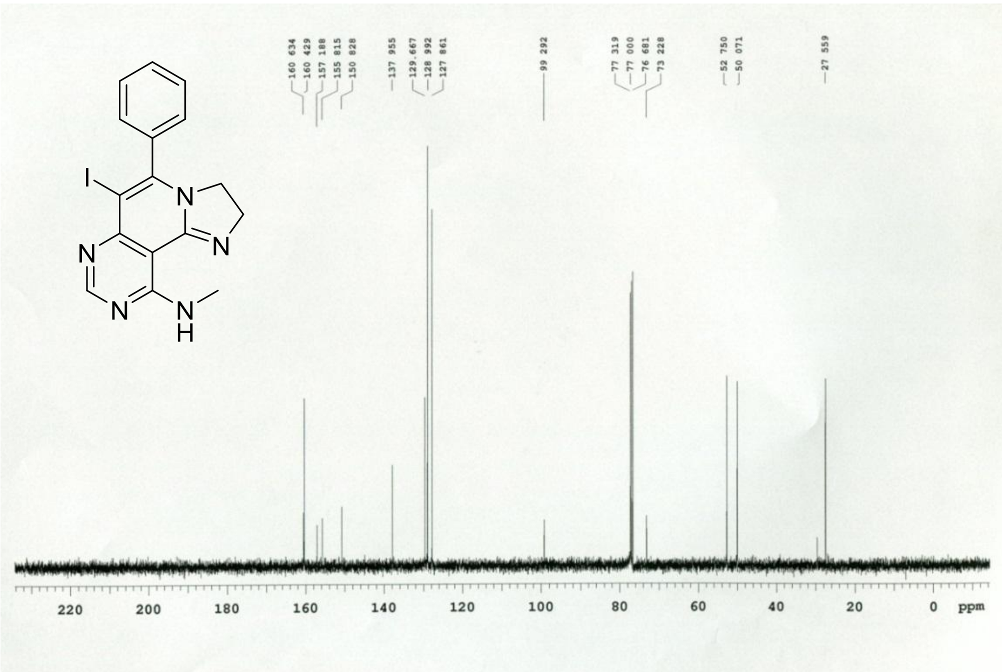
Compound 2f



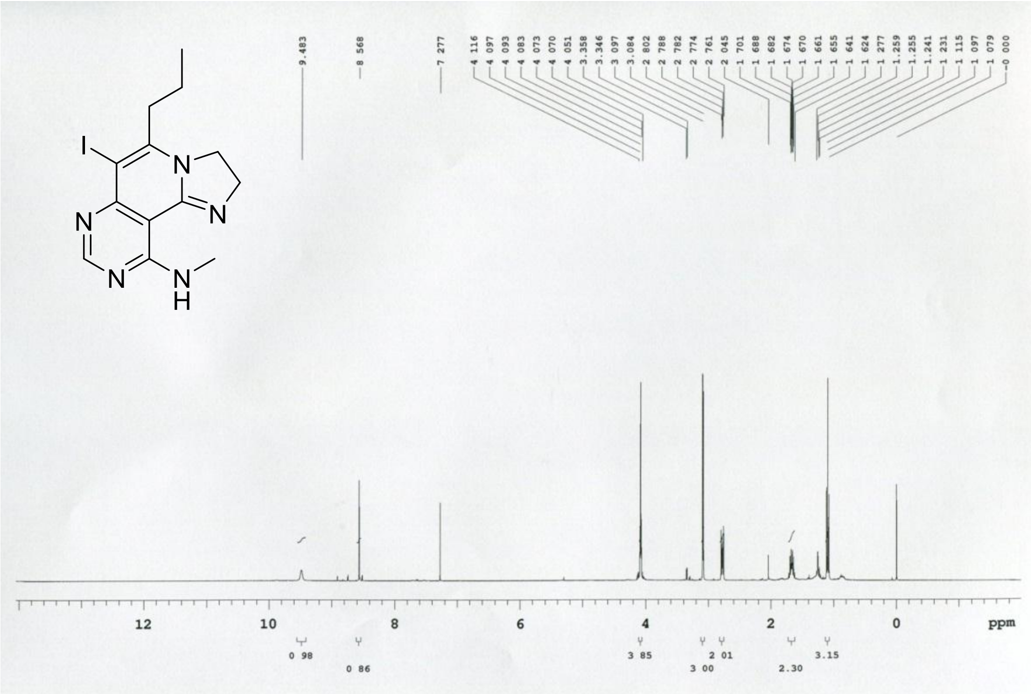


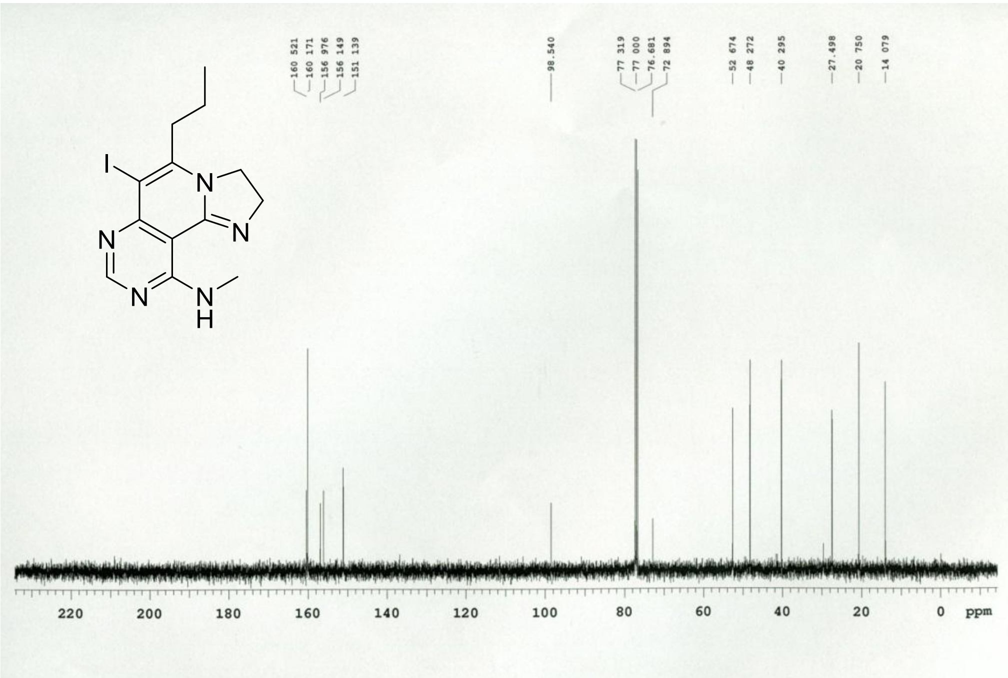
Compound 3a



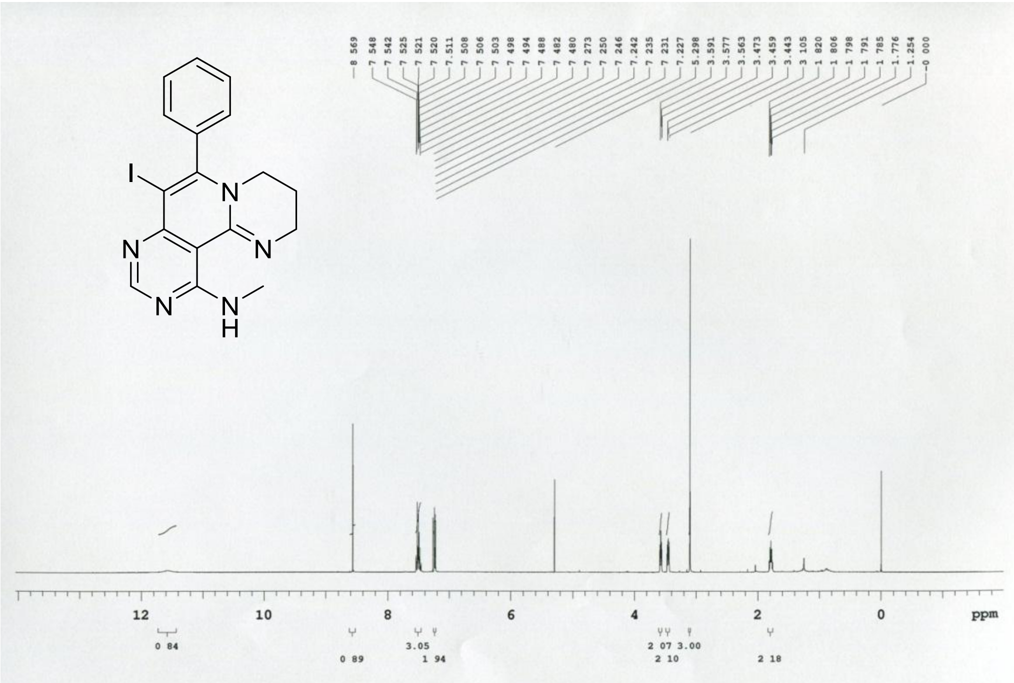


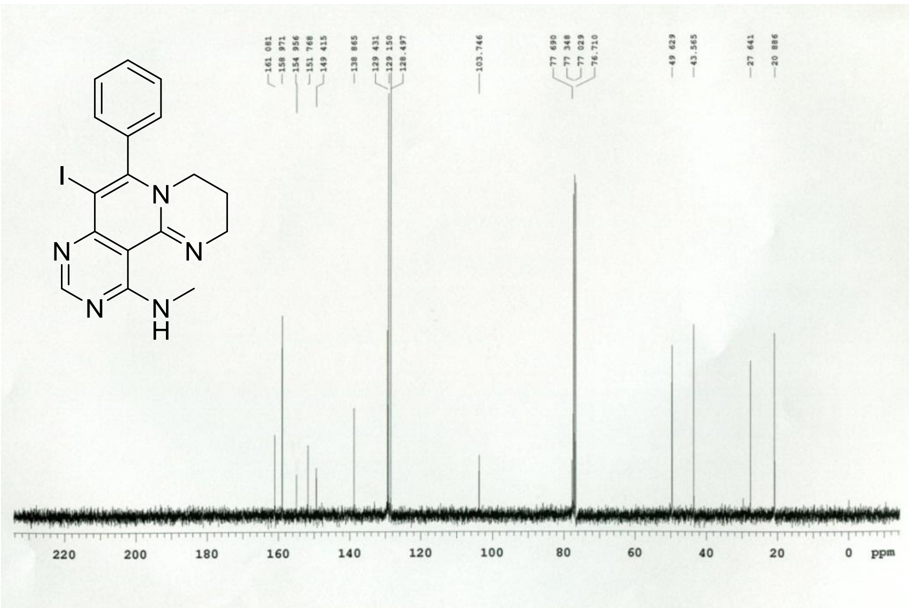
Compound 3b



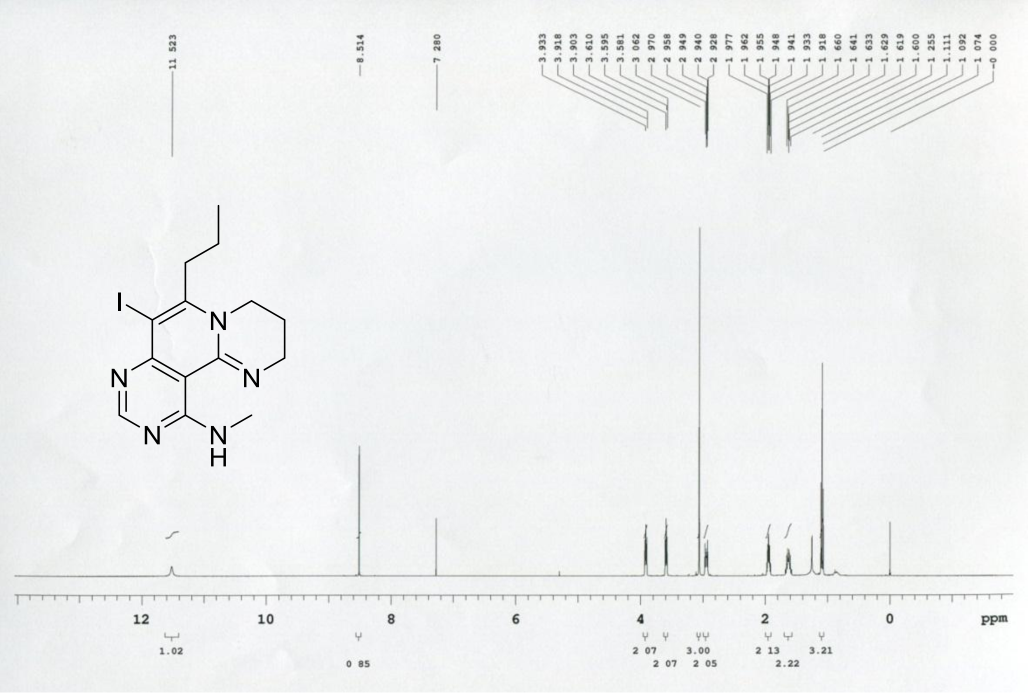


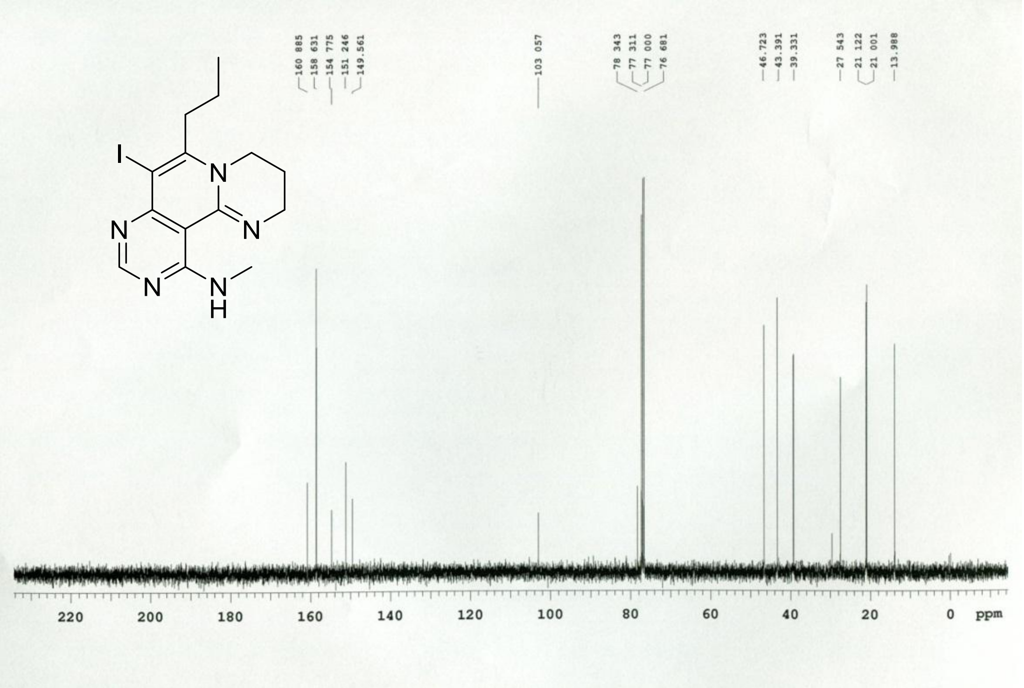
Compound 3c



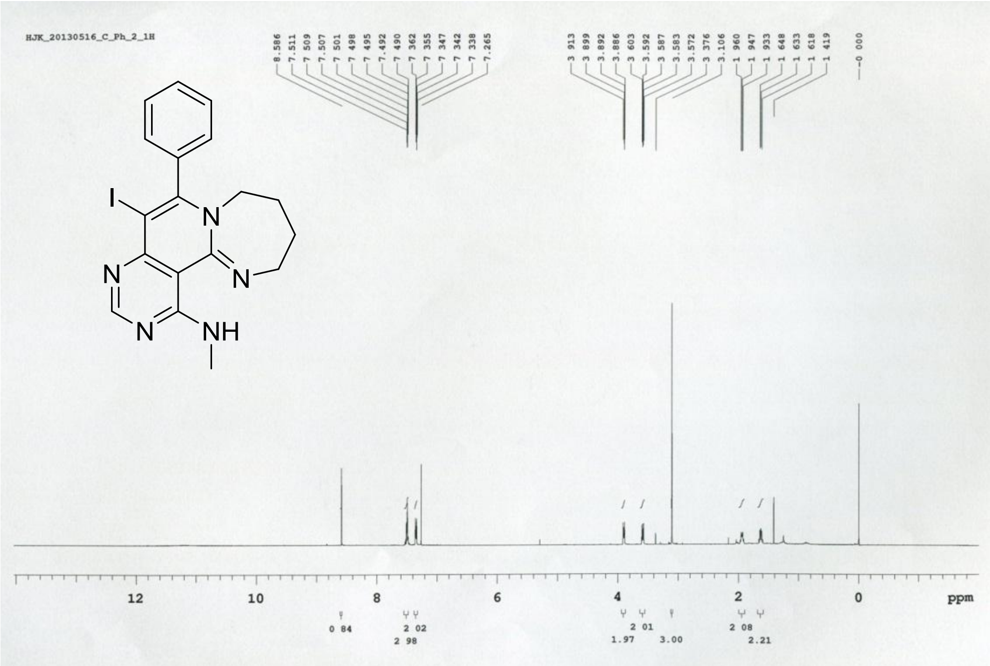


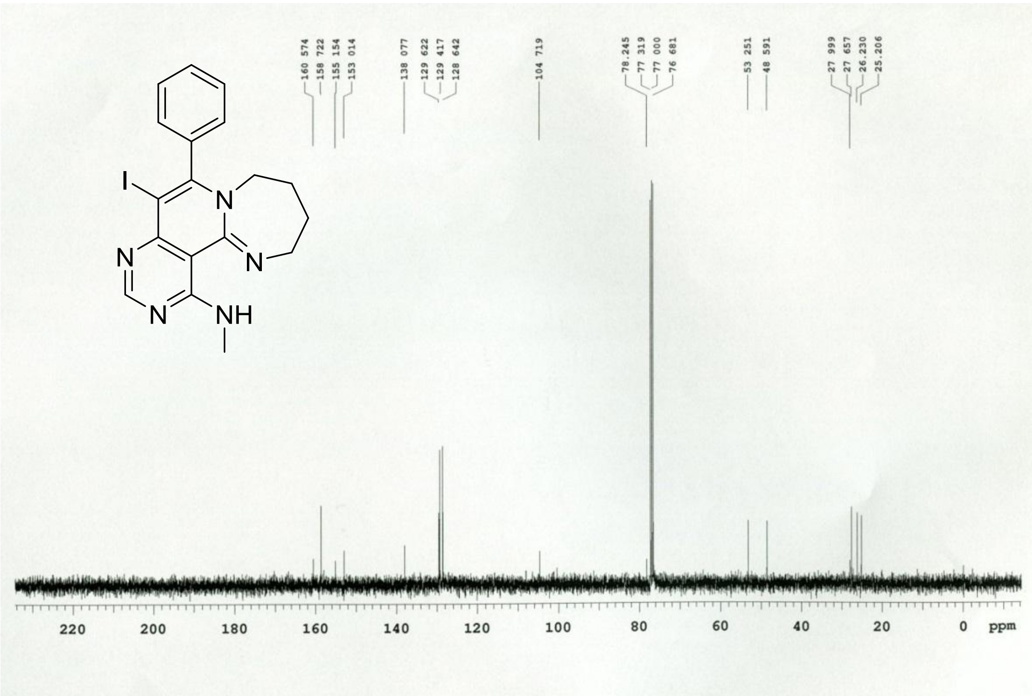
Compound 3d


11.523
8.514
7.280
3.933
3.918
3.903
3.610
3.595
3.581
3.062
2.970
2.958
2.949
2.940
2.928
1.977
1.962
1.955
1.948
1.941
1.933
1.918
1.660
1.641
1.633
1.629
1.619
1.600
1.255
1.111
1.092
1.074
0.000
I
N
N
N
N
N
H
12
10
8
6
4
2
0
ppm
1.02
0.85
2.07
2.07
3.00
2.05
2.13
2.22
3.21

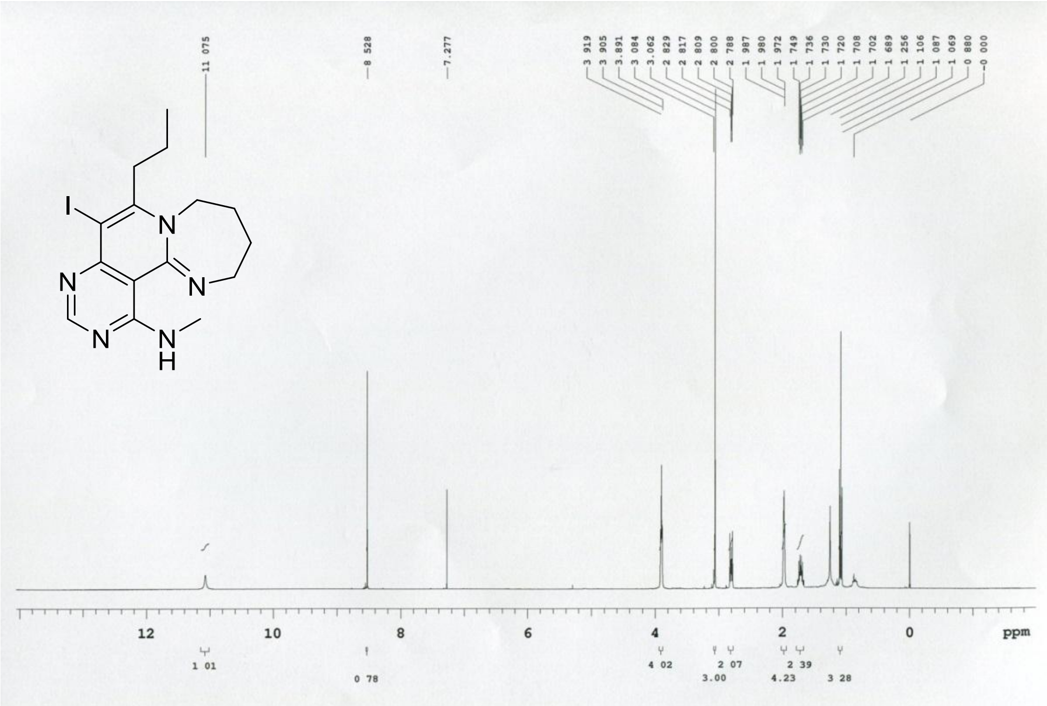

160.885
158.631
154.775
151.246
149.561
103.057
78.343
77.311
77.000
76.681
46.723
43.391
39.331
27.543
21.122
21.001
13.988
I
N
N
N
N
N
H
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound 3e

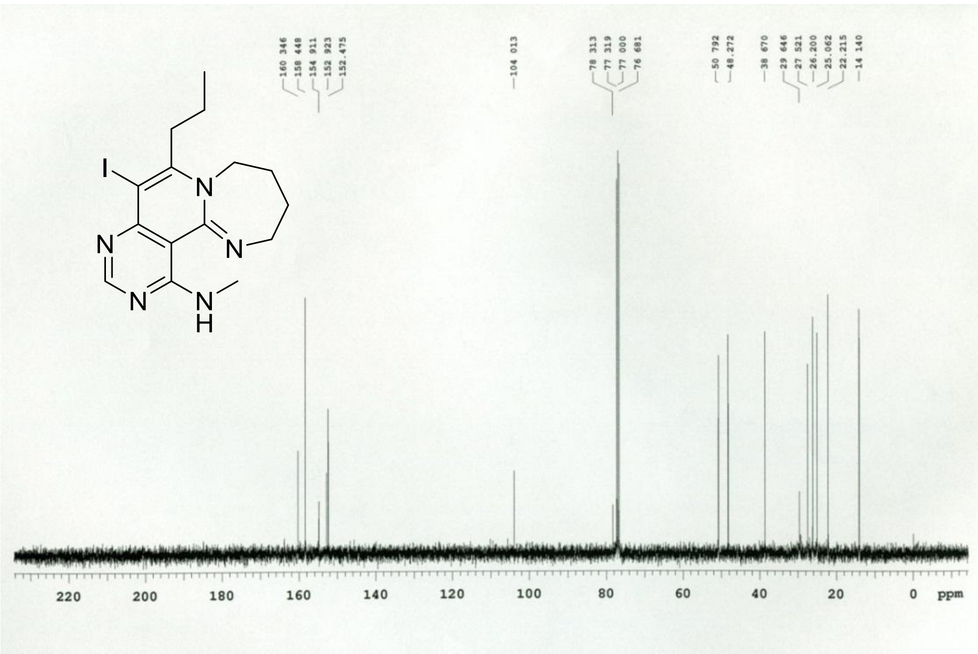




Compound 3f

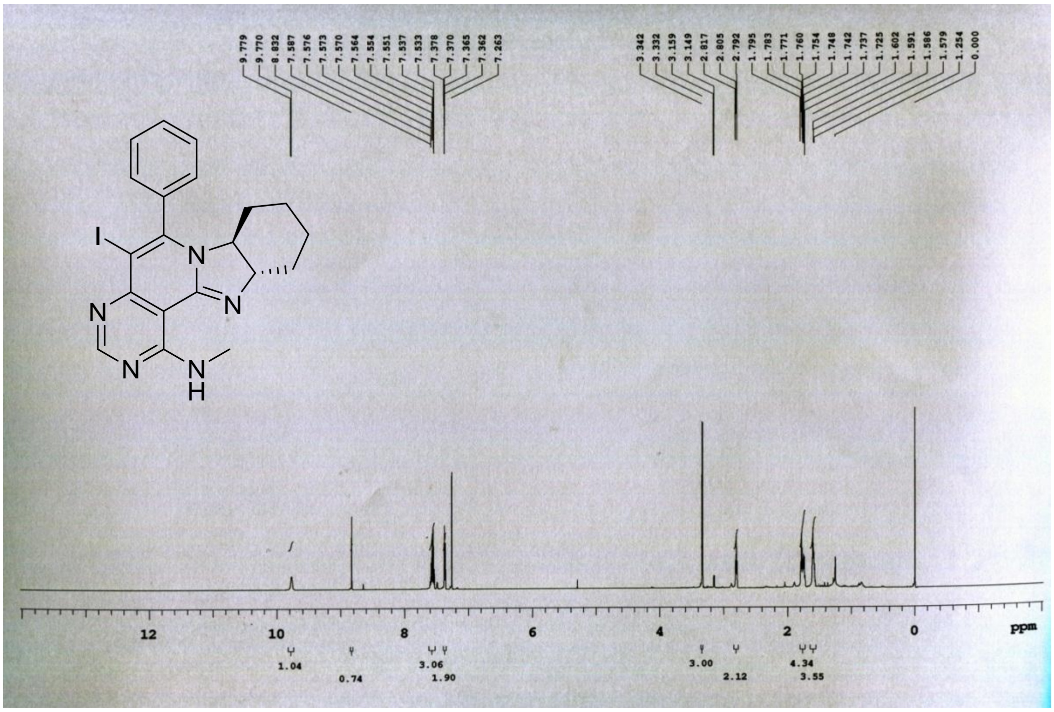


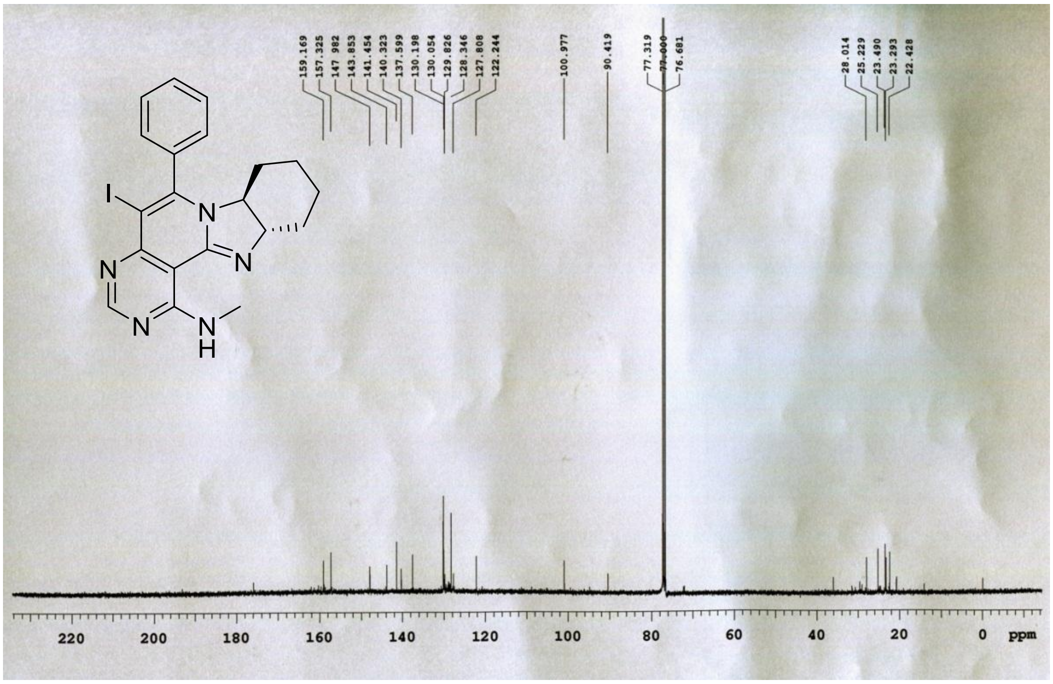
11.075
8.528
7.277
3.919
3.905
3.891
3.084
3.062
2.829
2.817
2.809
2.800
2.788
1.987
1.980
1.972
1.749
1.736
1.730
1.720
1.708
1.702
1.689
1.256
1.106
1.087
1.069
0.880
0.000
12
10
8
6
4
2
0
ppm
1.01
0.78
4.02
3.00
2.07
4.23
2.39
3.28



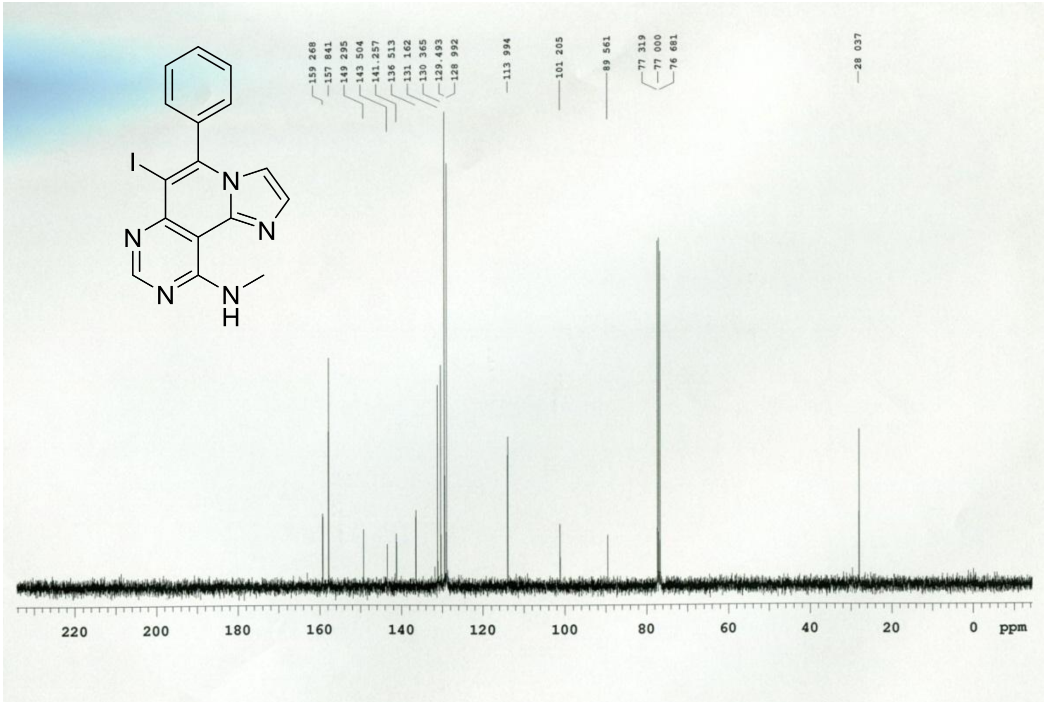
160.346
158.448
154.911
152.923
152.475
104.013
78.313
77.319
77.000
76.681
50.792
48.272
38.670
29.646
27.521
26.200
25.062
22.215
14.140
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound 3g

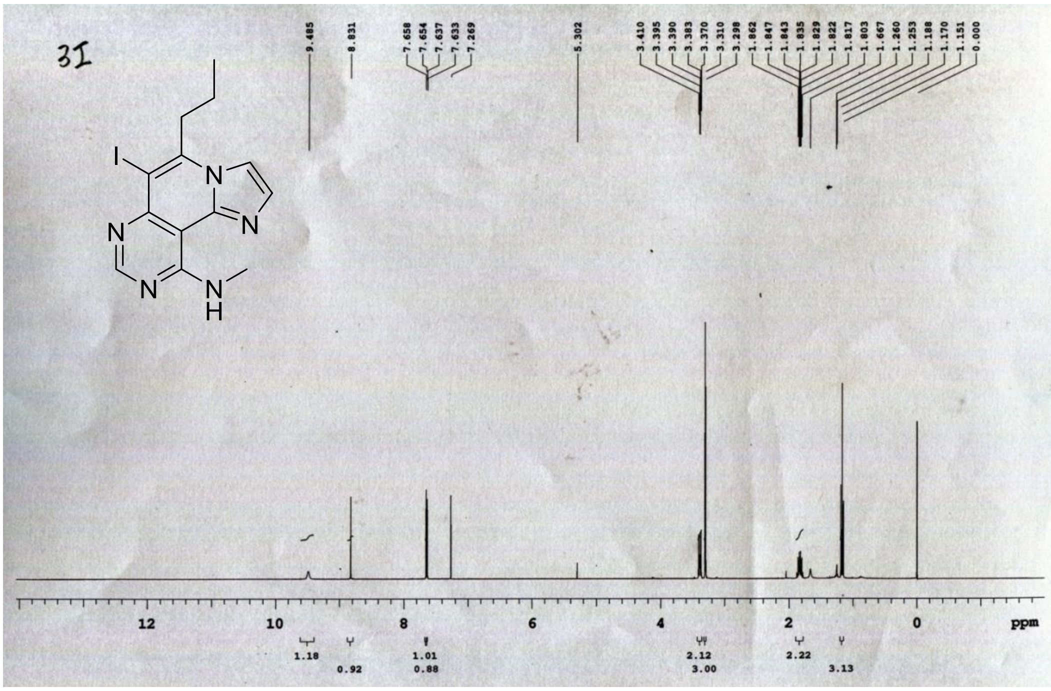


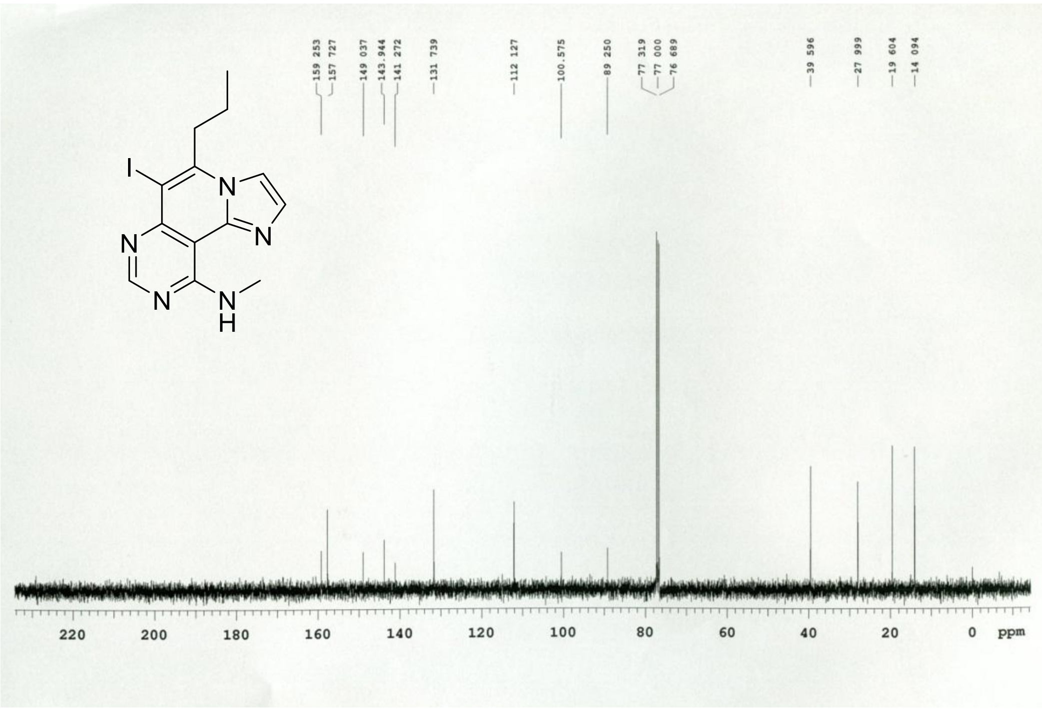


Compound 3h

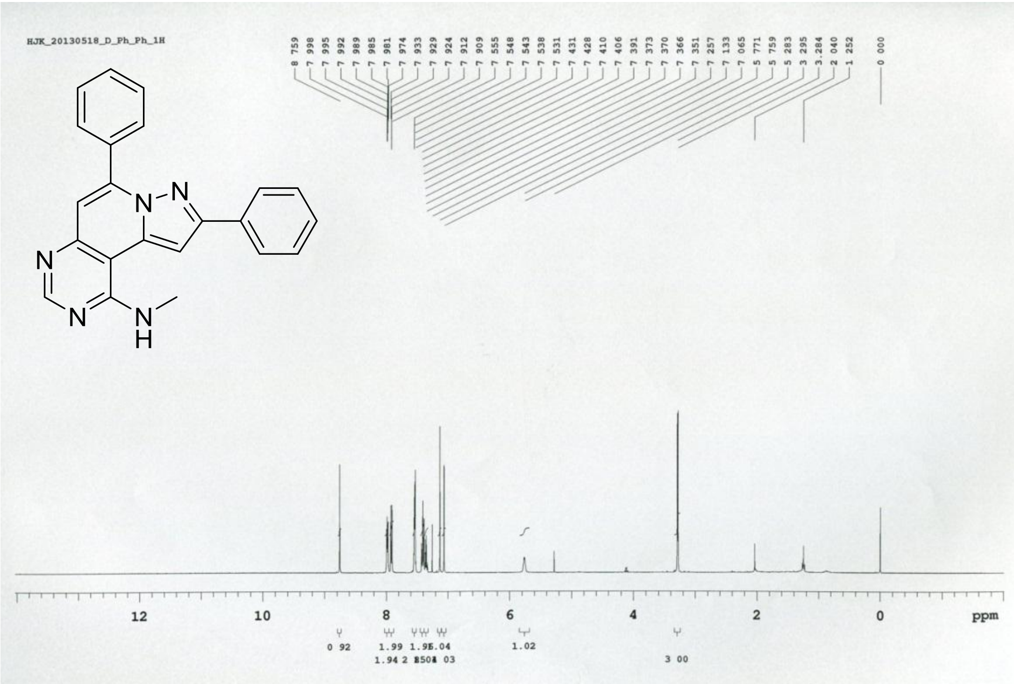


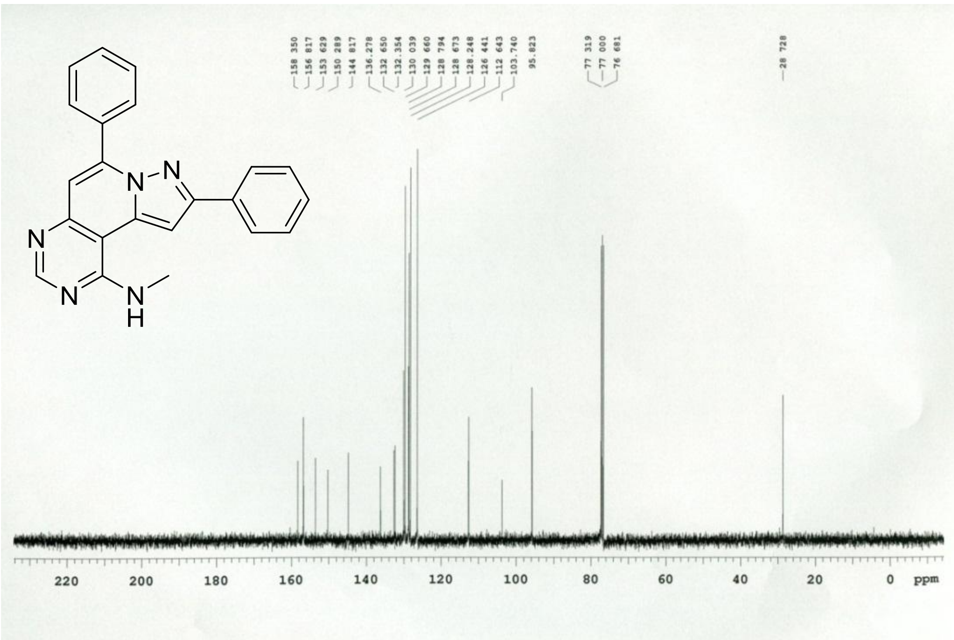
Compound 3i


3I
I
N
N
N
N
N
H
9.485
8.831
7.658
7.654
7.637
7.633
7.269
5.302
3.410
3.395
3.390
3.383
3.370
3.310
3.298
1.862
1.847
1.843
1.835
1.829
1.822
1.817
1.803
1.667
1.260
1.253
1.188
1.170
1.151
0.000
12
10
8
6
4
2
0
ppm
1.18
0.92
1.01
0.88
2.12
3.00
2.22
3.13

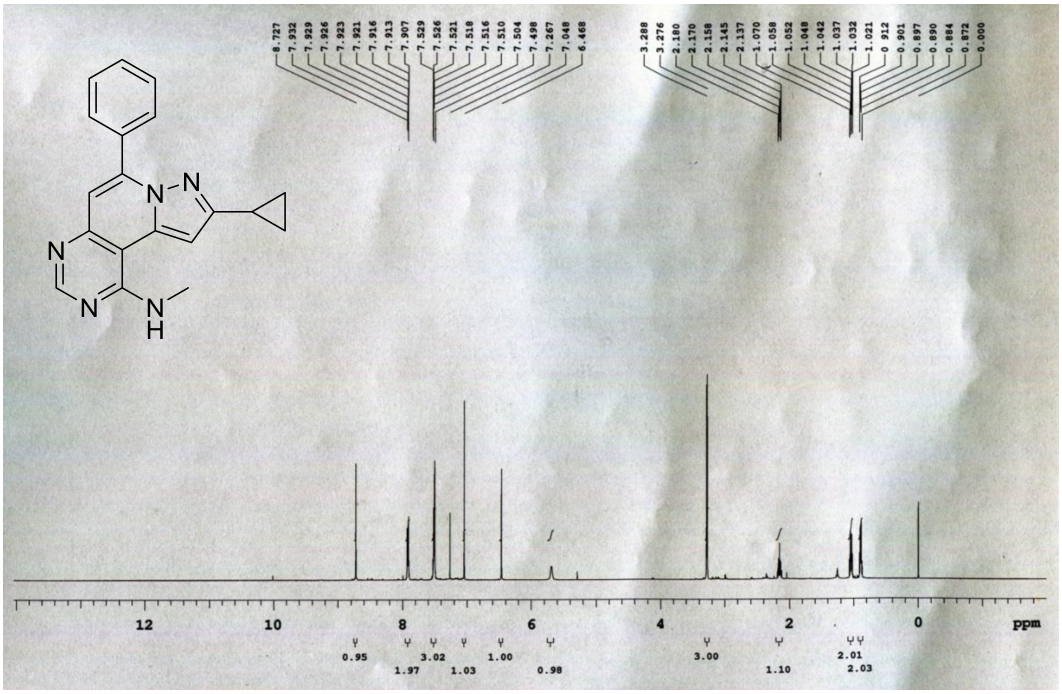

I
N
N
N
N
N
H
159 253
157 727
149 037
143.944
141 272
131 739
112 127
100.575
89 250
77 319
77 000
76 689
39 596
27 999
19 604
14 094
220
200
180
160
140
120
100
80
60
40
20
0
ppm

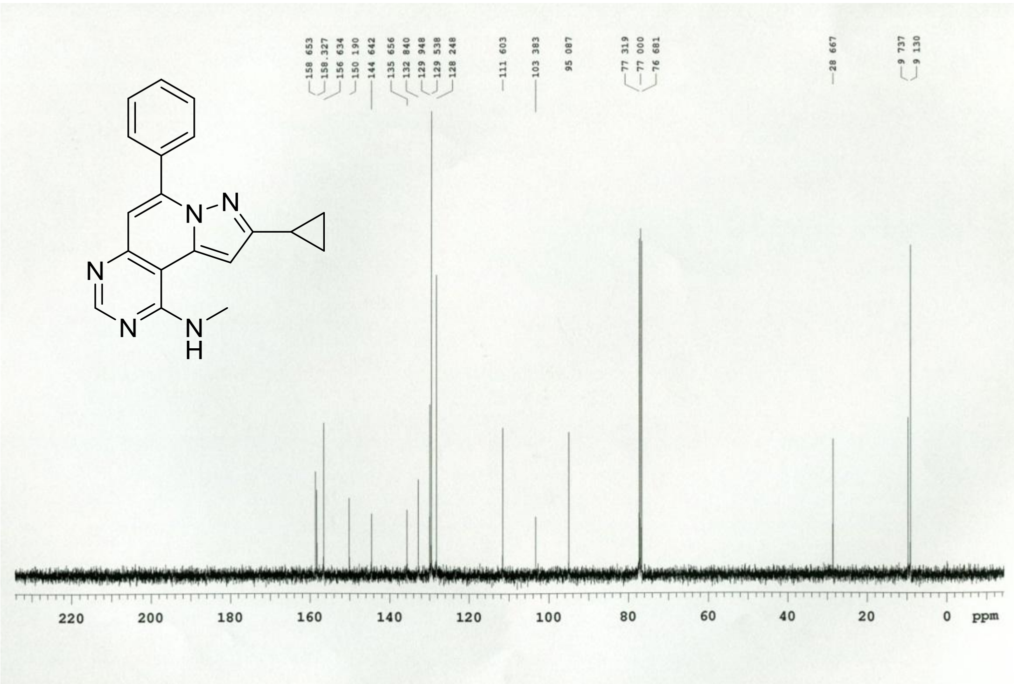
Compound 4a



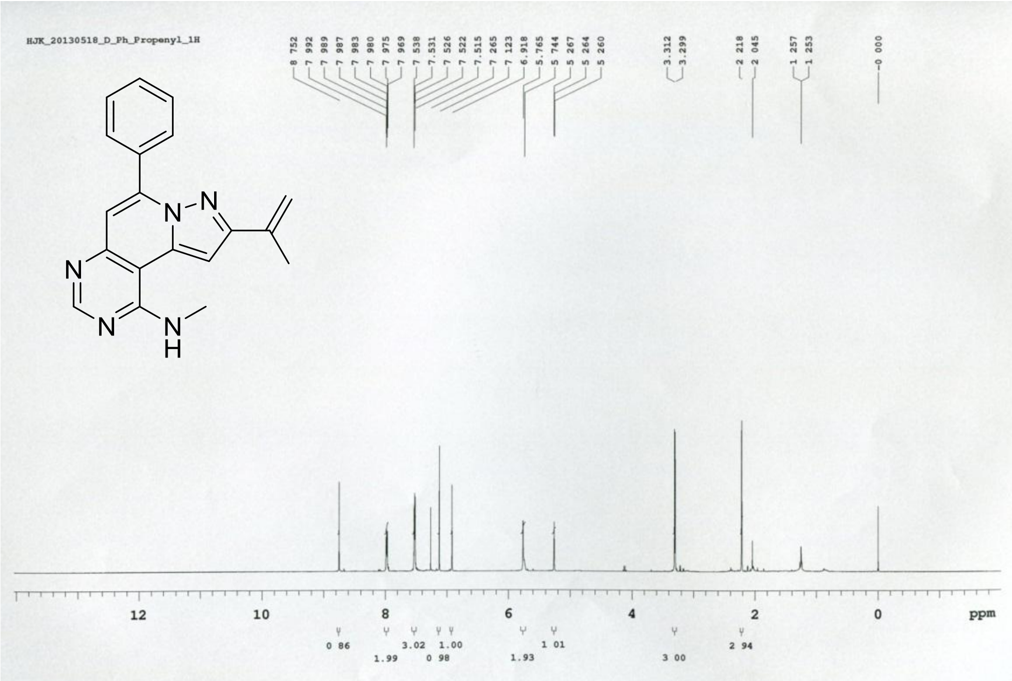


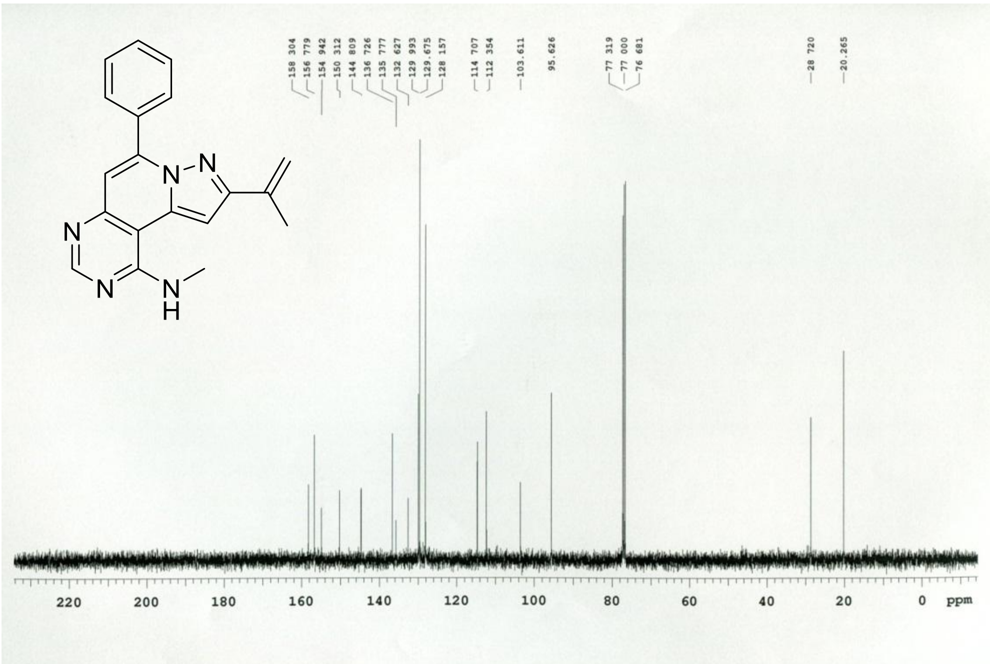
Compound 4b



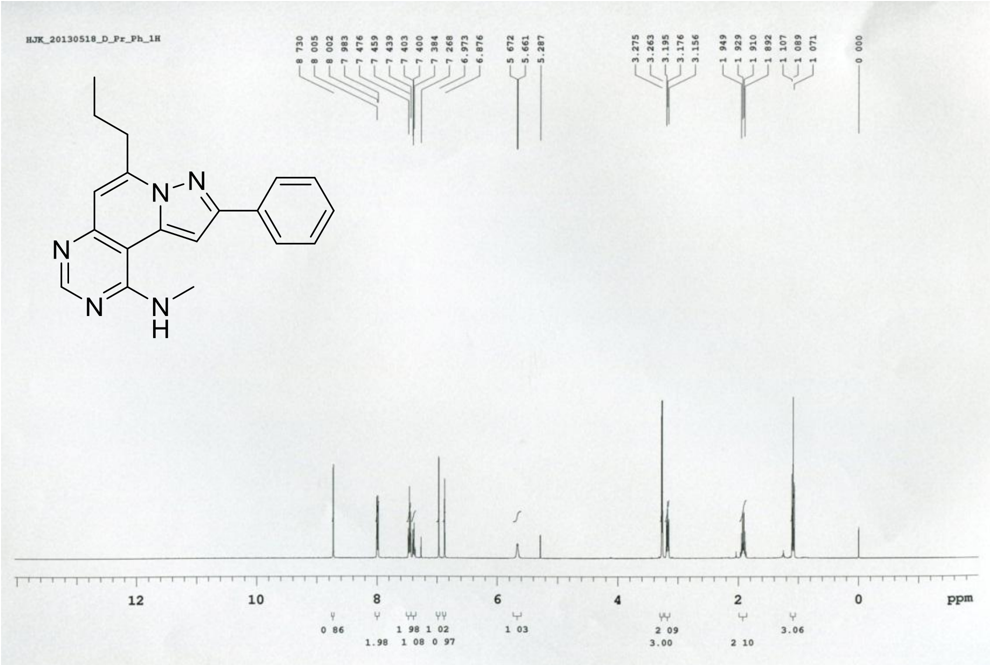


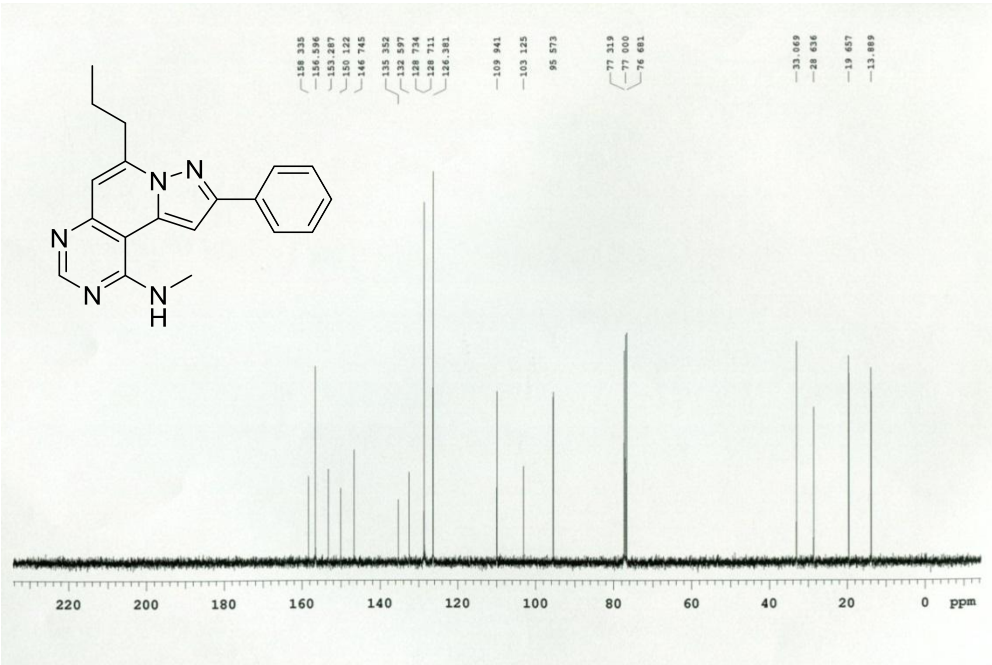
Compound 4c



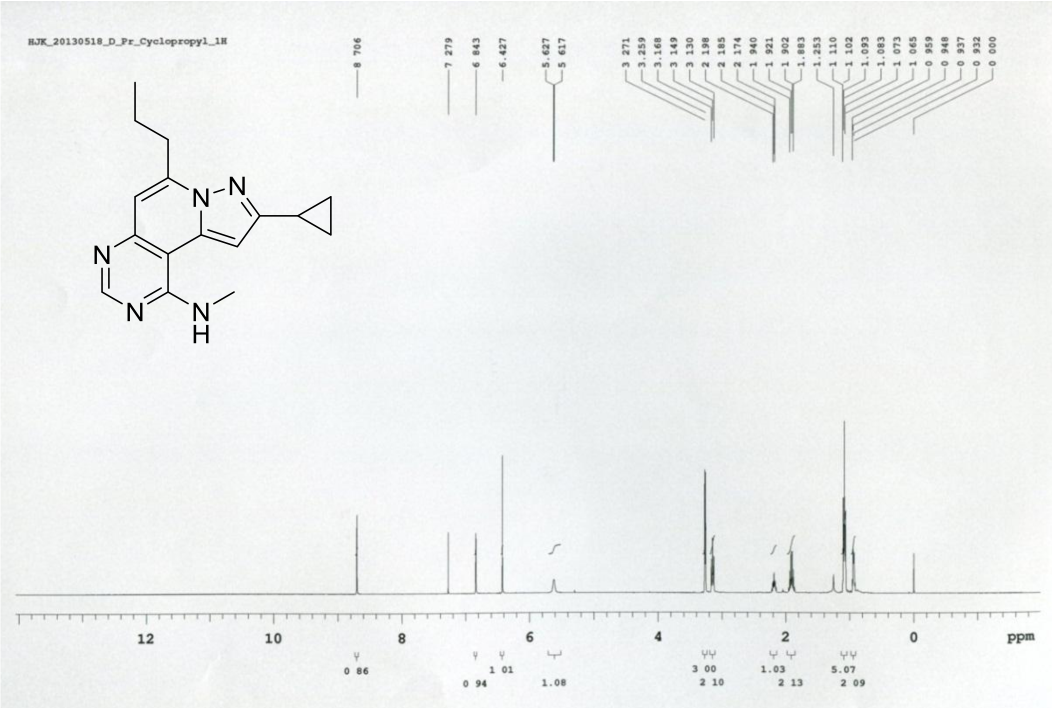


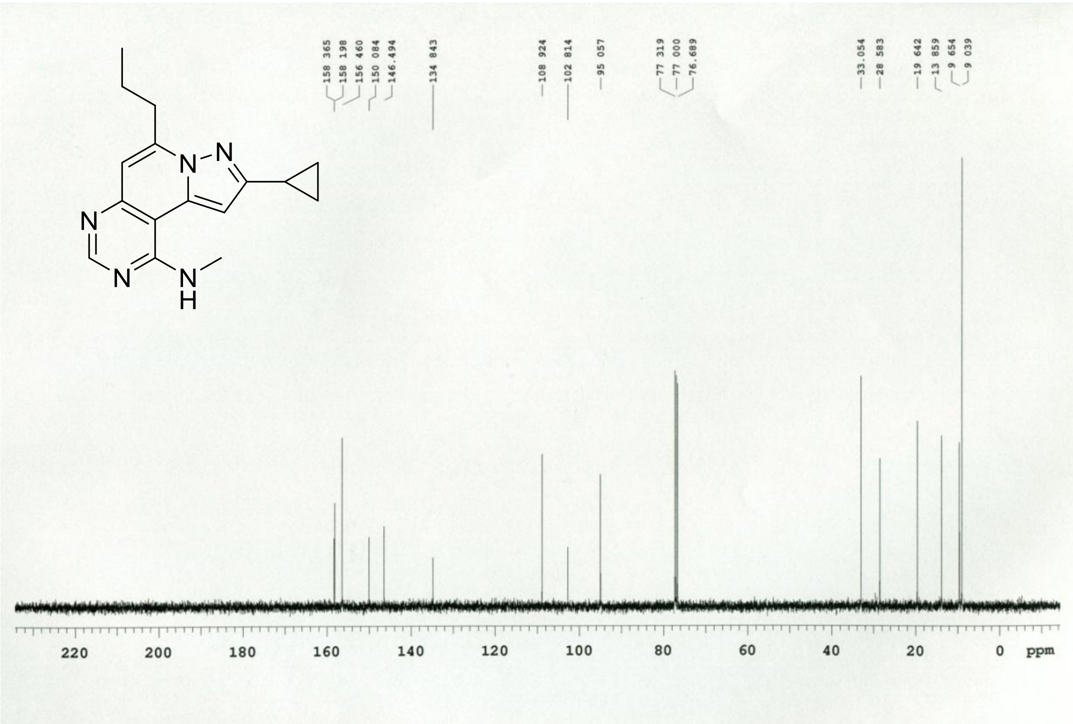
Compound 4d



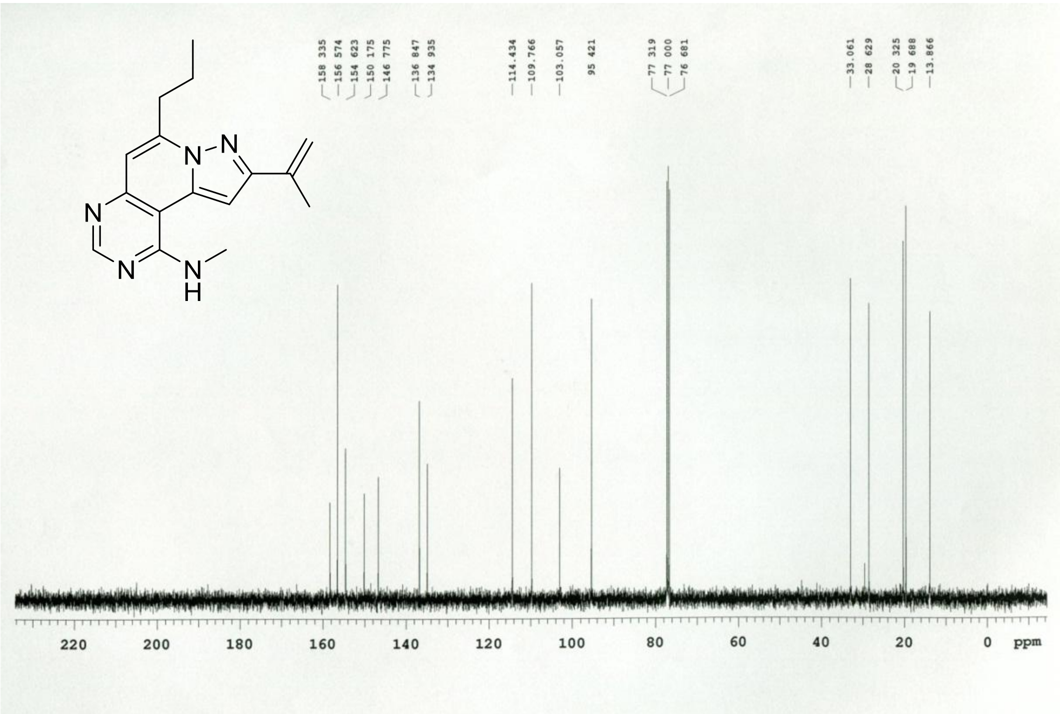


Compound 4e

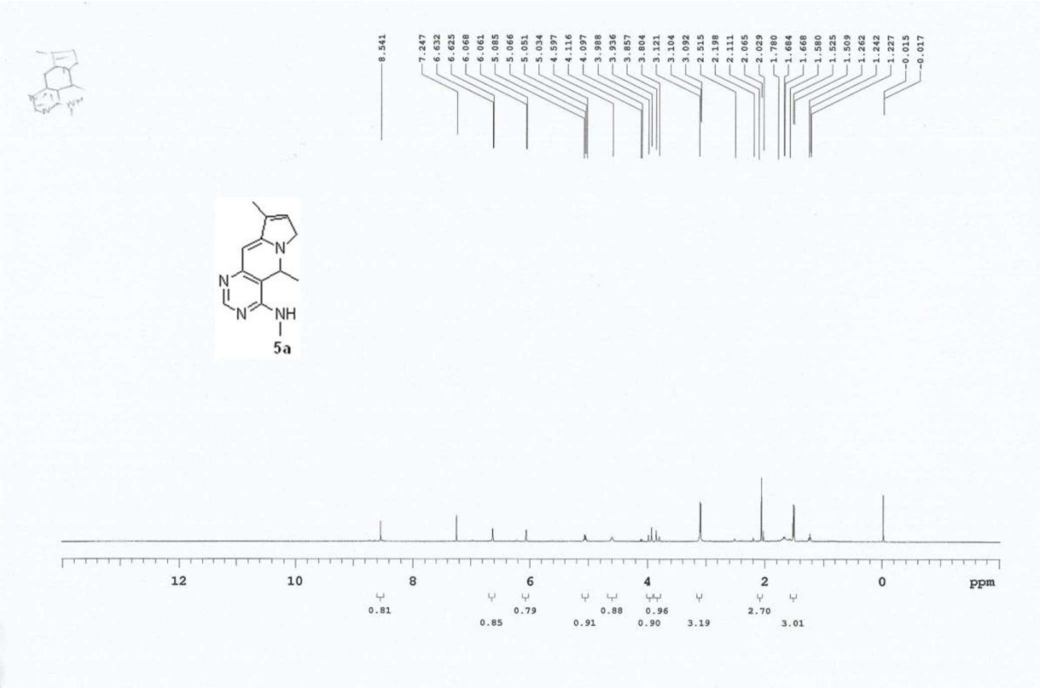


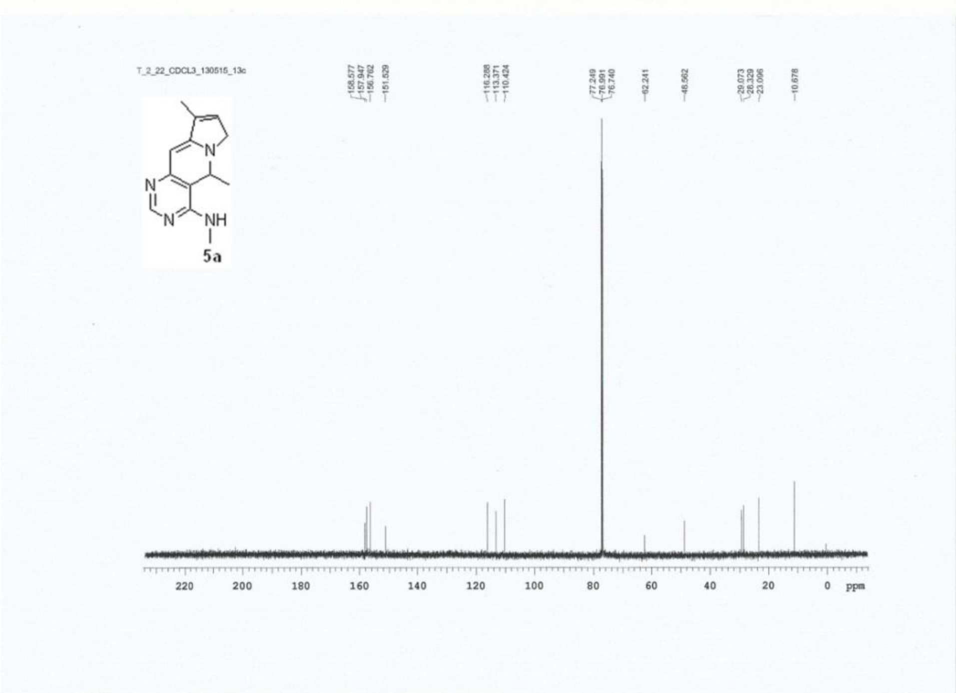


Compound 4f

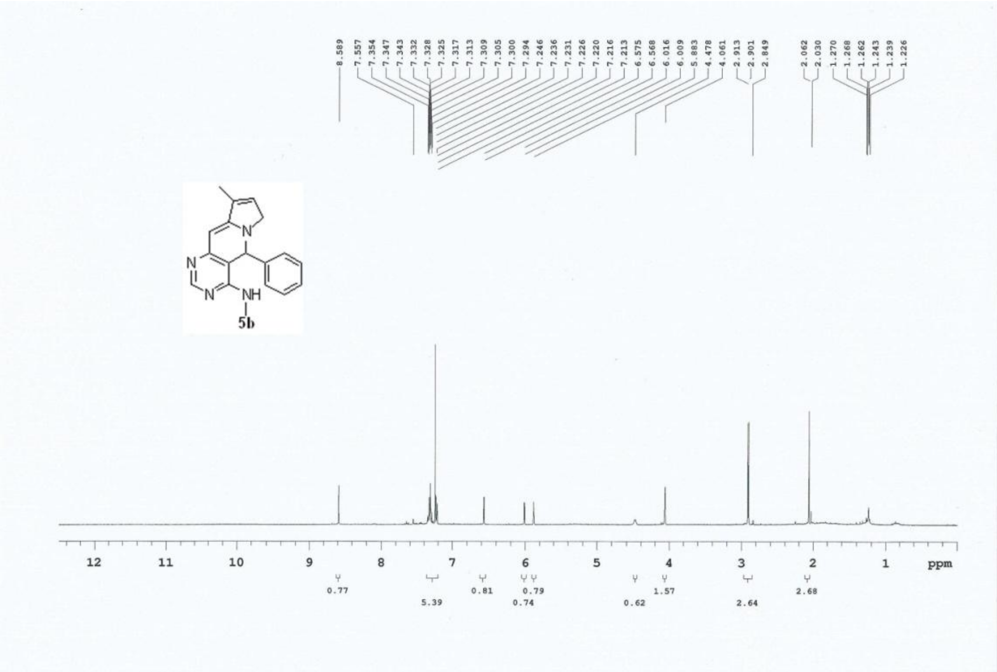


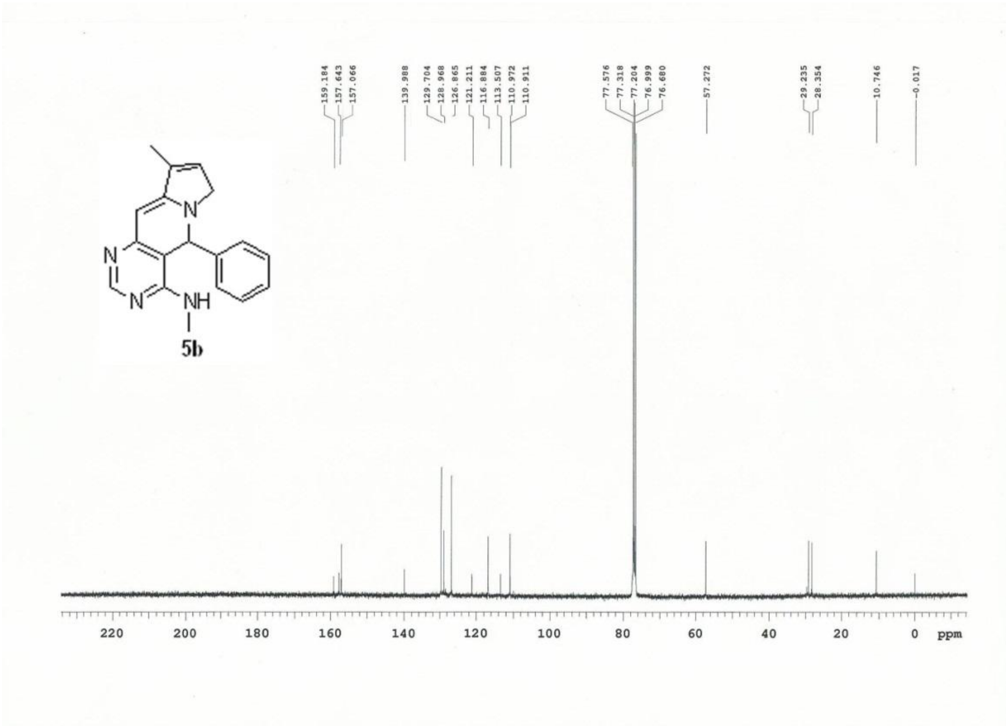
Compound 5a



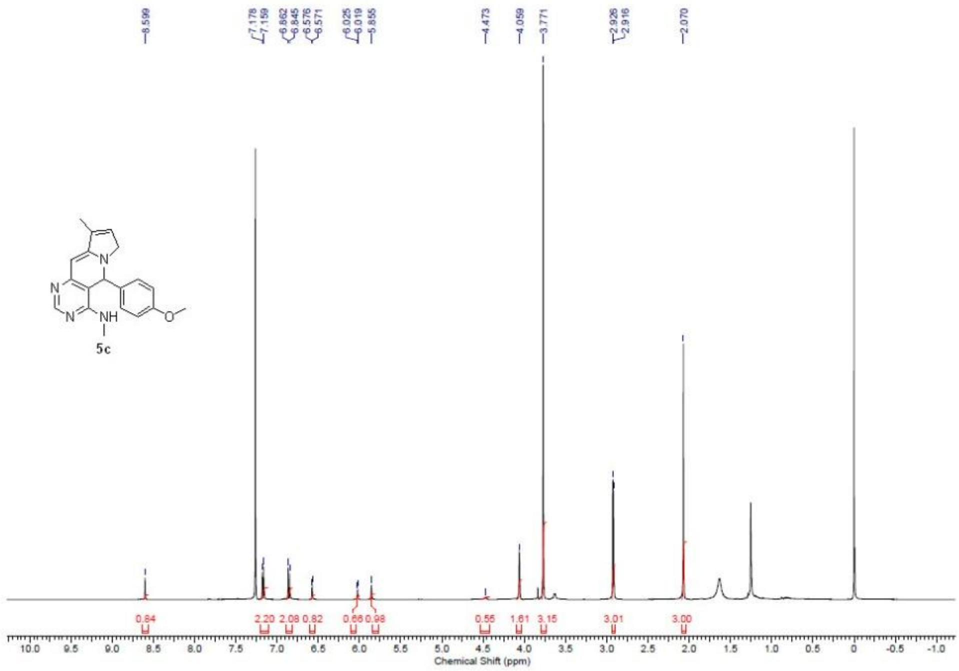


Compound 5b

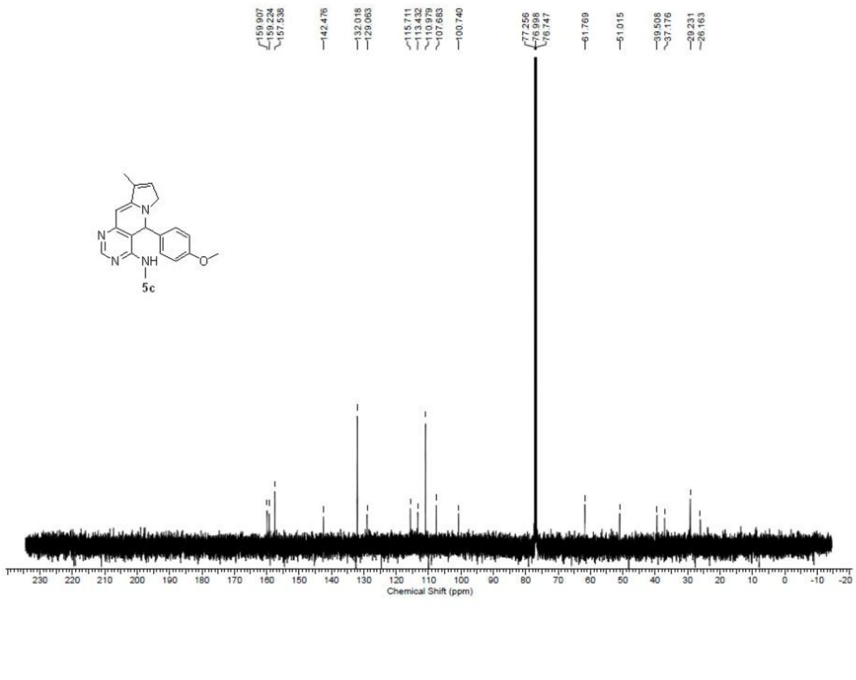




Compound 5c

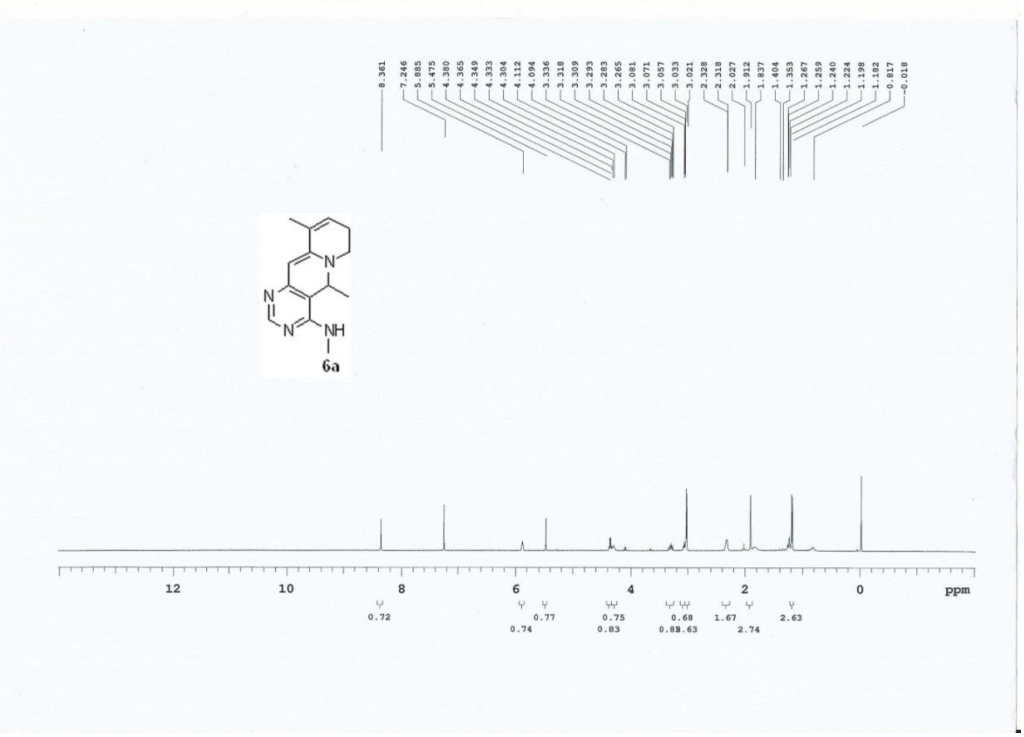


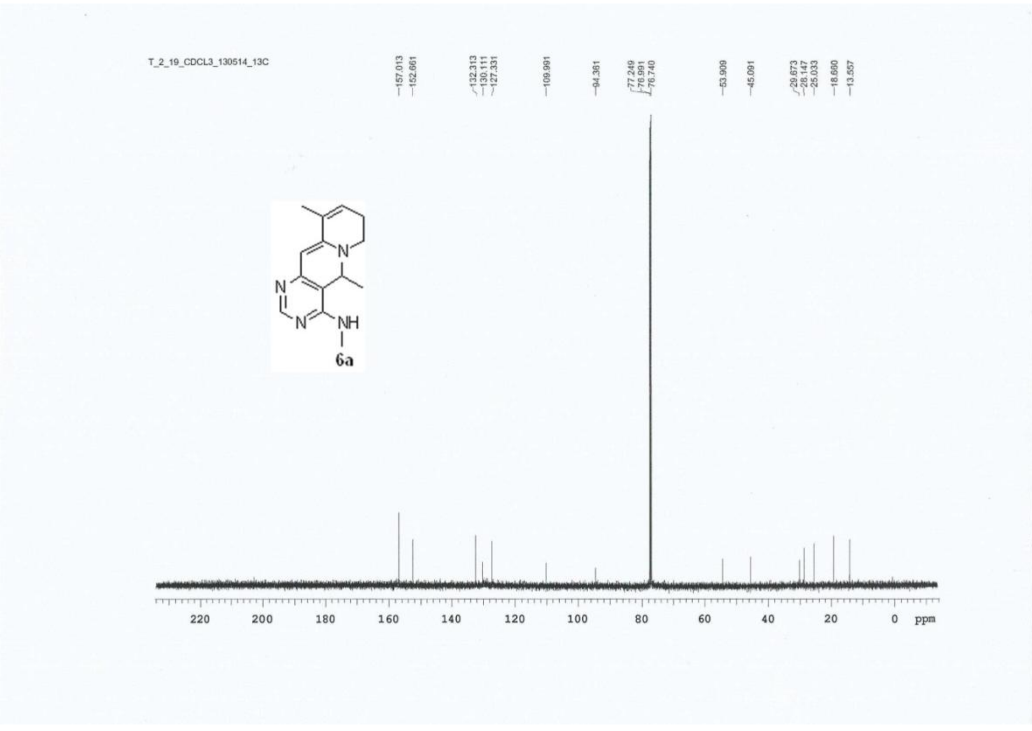
8.599
7.178
7.159
6.862
6.845
6.576
6.571
6.025
6.019
5.855
4.473
4.059
3.771
2.926
2.916
2.070
N
N
NH
N
O
5c
0.84
2.20
2.08
0.82
0.66
0.98
0.55
1.61
3.15
3.01
3.00
Chemical Shift (ppm)



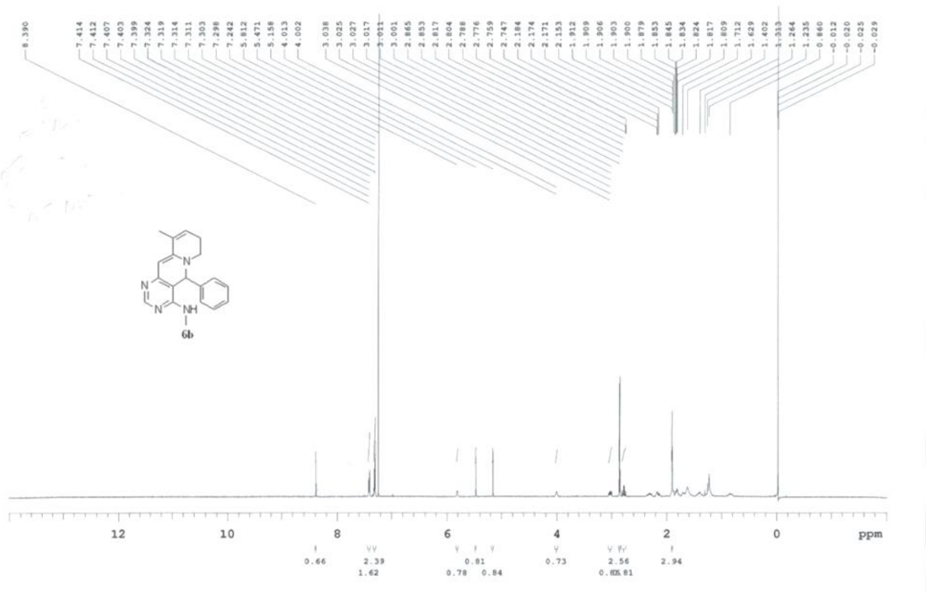
159.907
159.224
157.538
142.476
132.018
129.063
115.711
113.432
110.979
107.683
100.740
77.256
76.998
76.747
61.769
51.015
39.508
37.176
29.231
26.163
N
N
NH
N
O
5c
Chemical Shift (ppm)

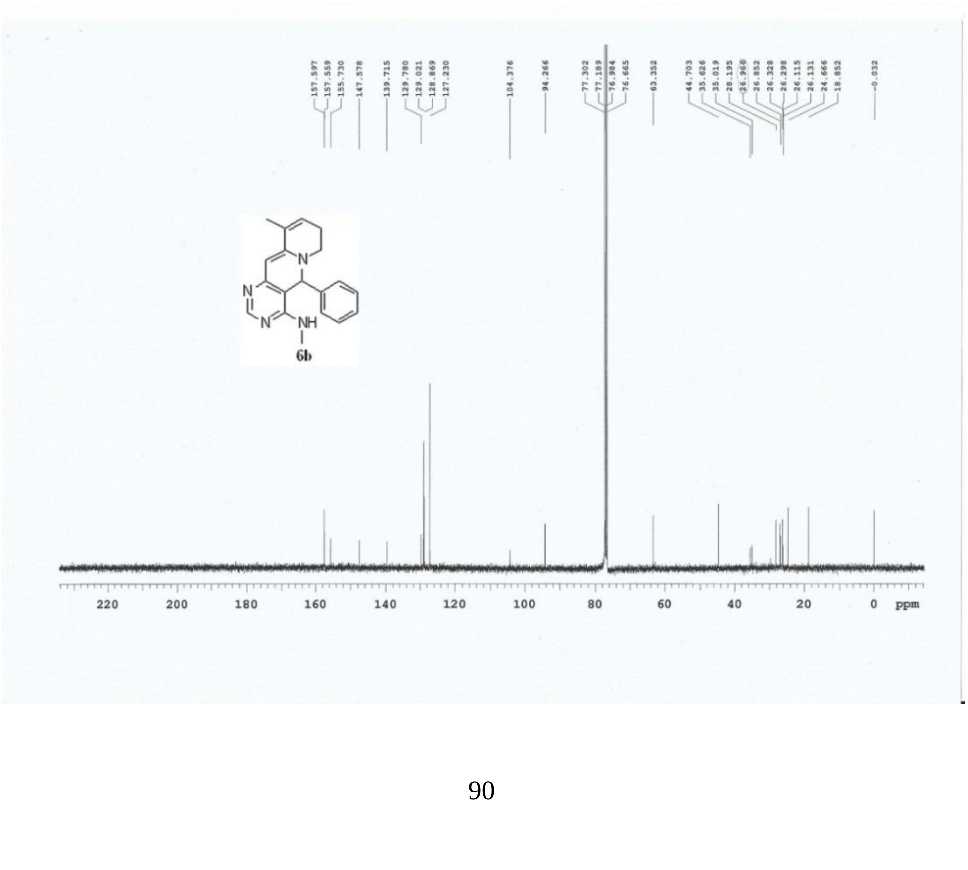
Compound 6a



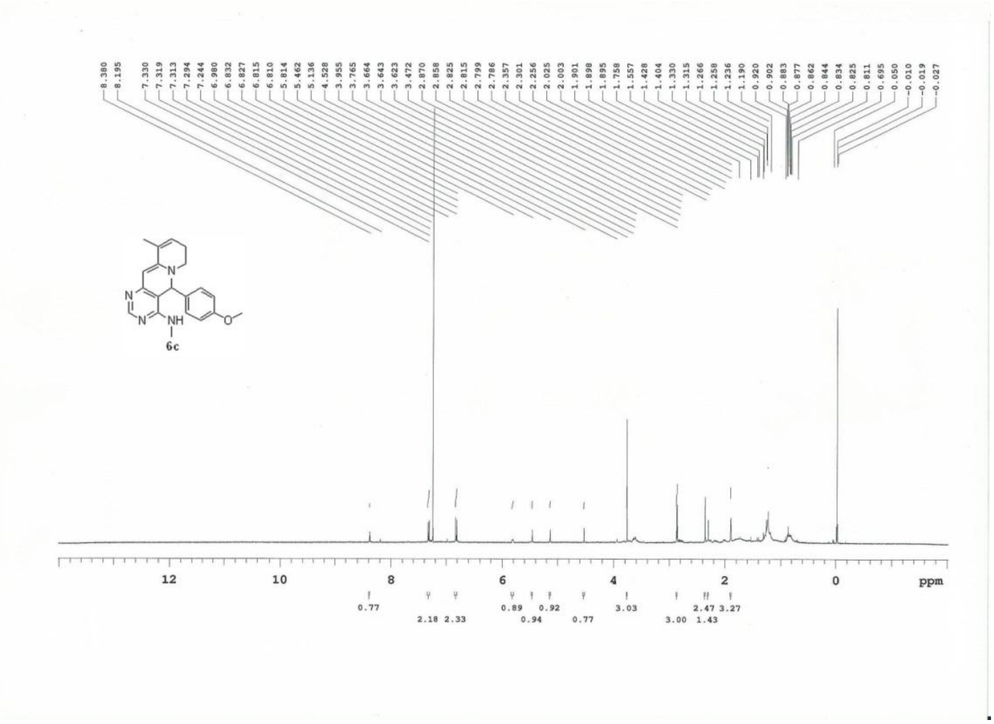


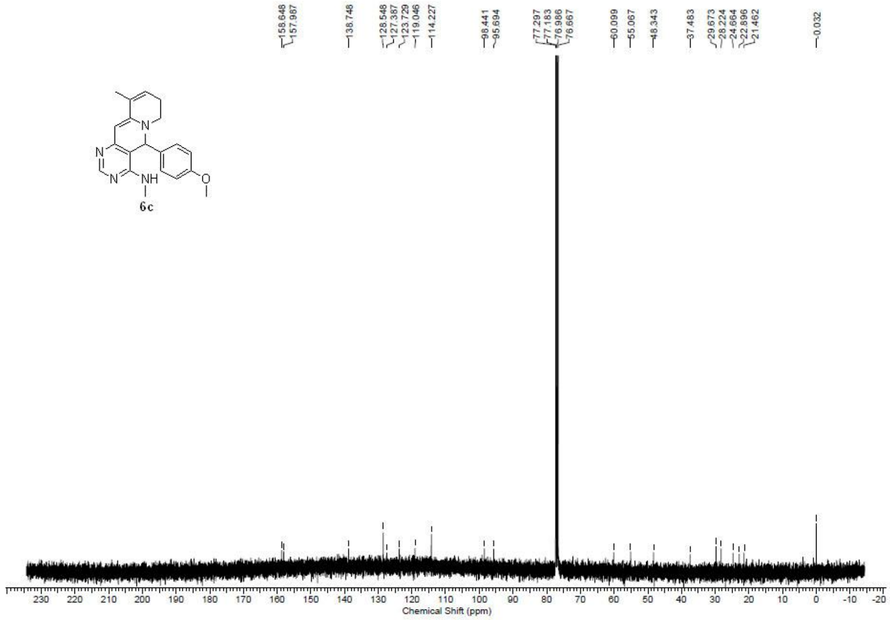
Compound 6b



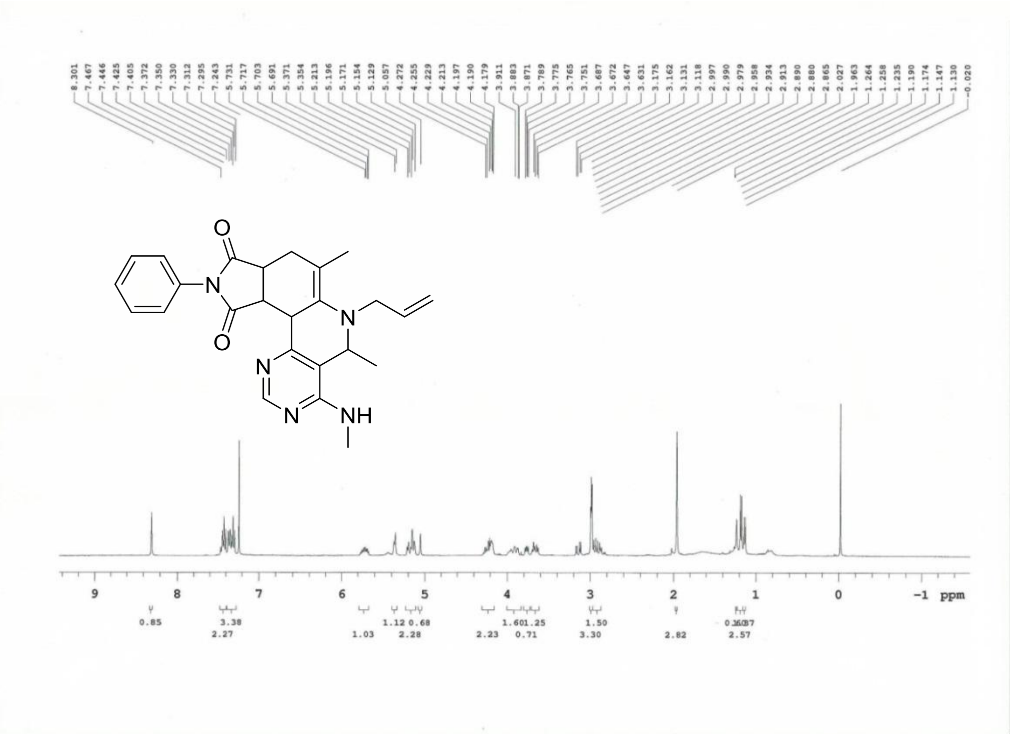


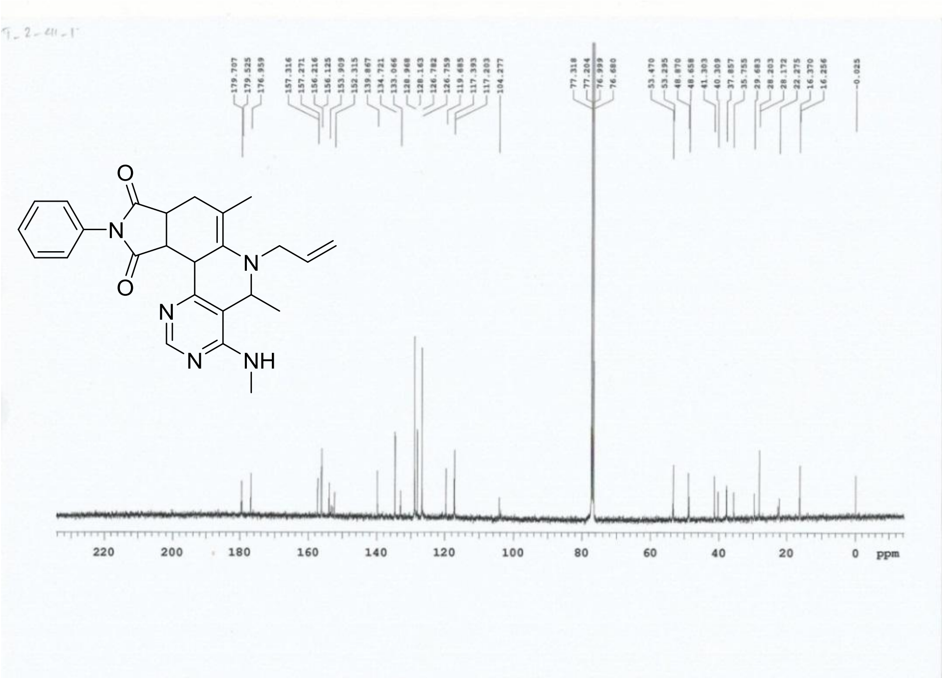
Compound 6c



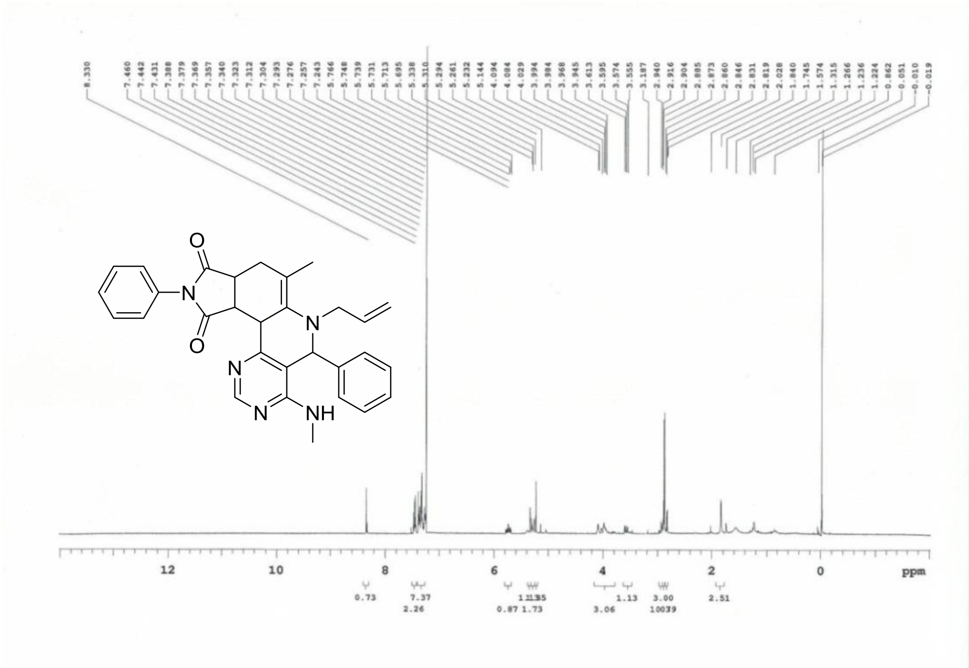


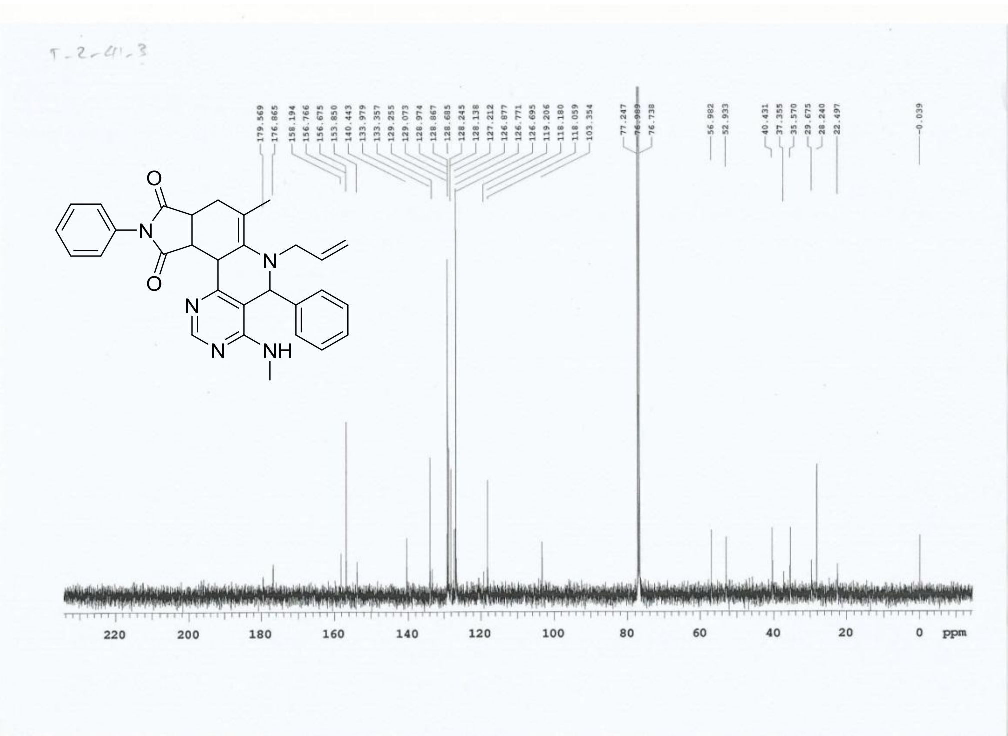
Compound 7a



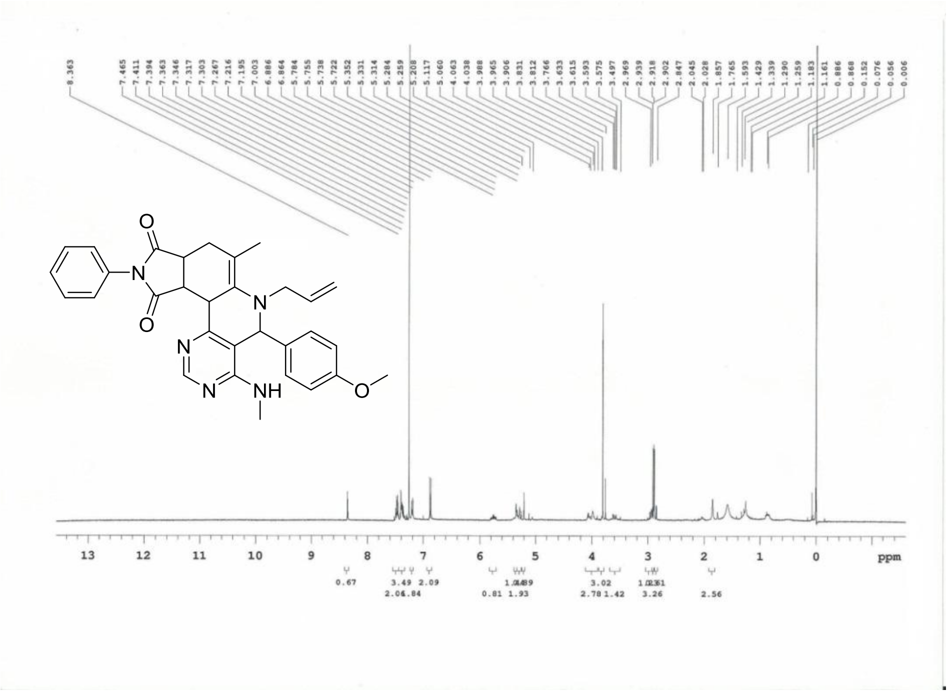


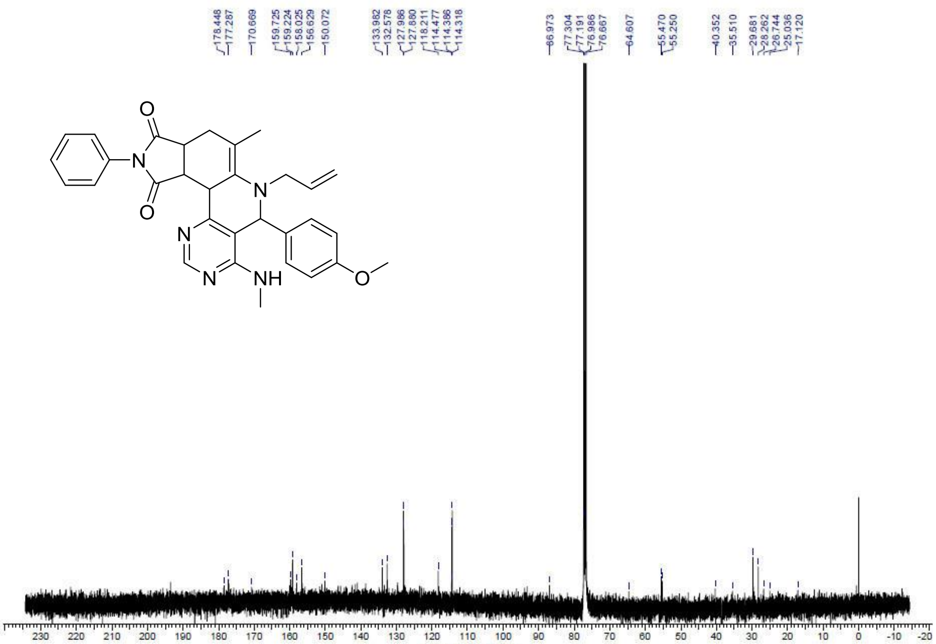
Compound 7b



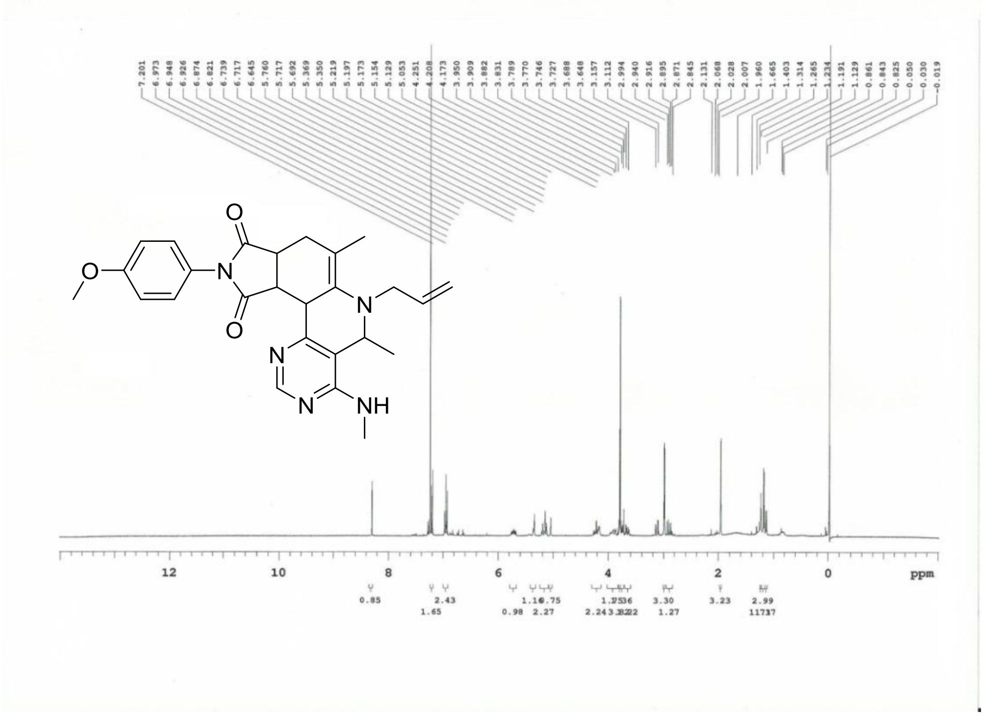


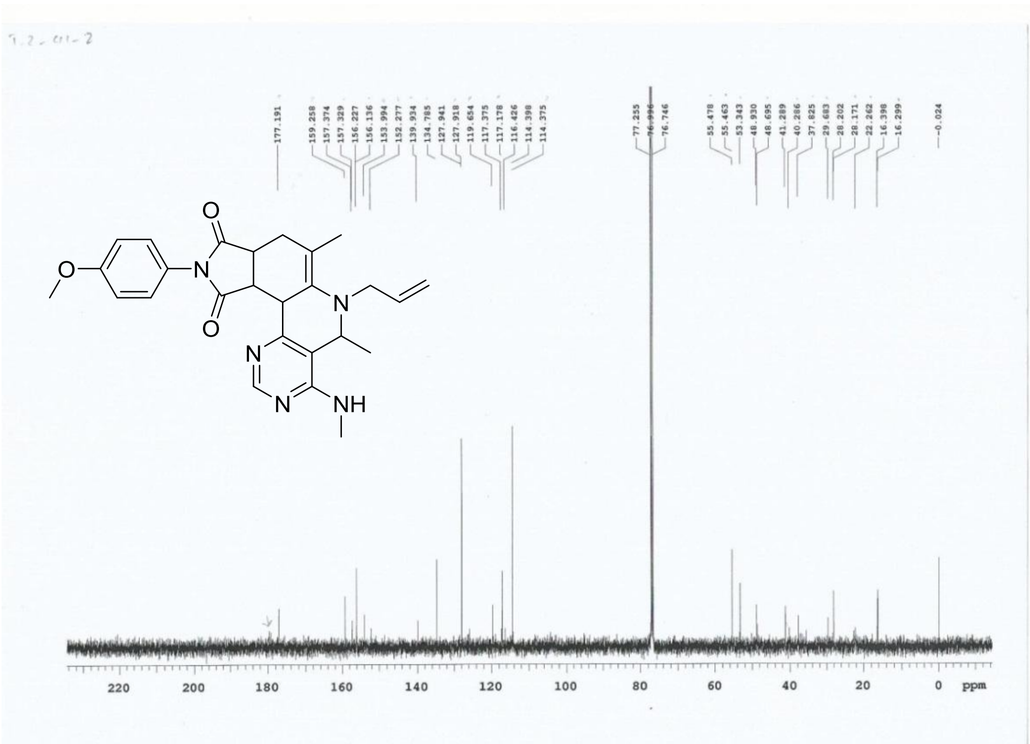
Compound 7c



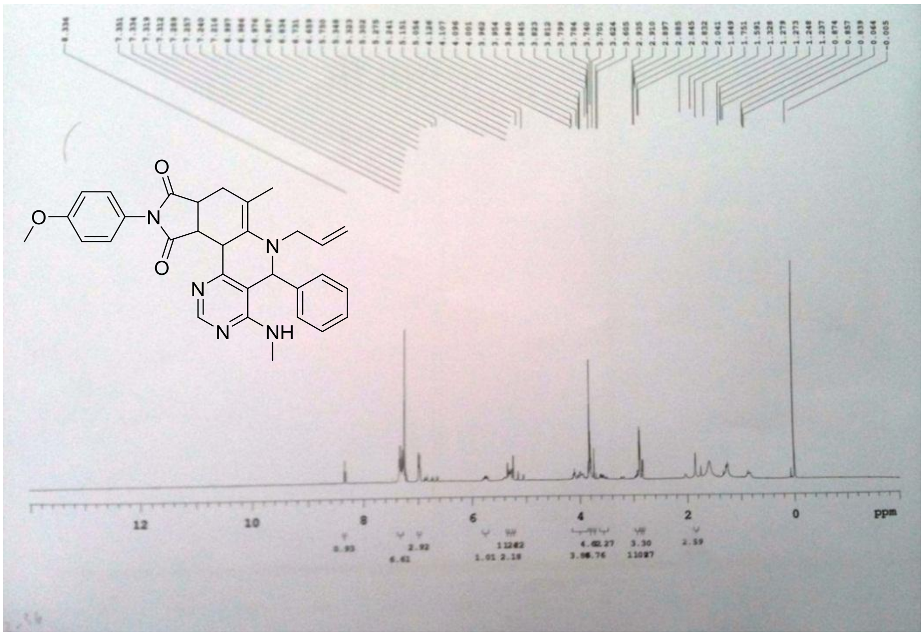


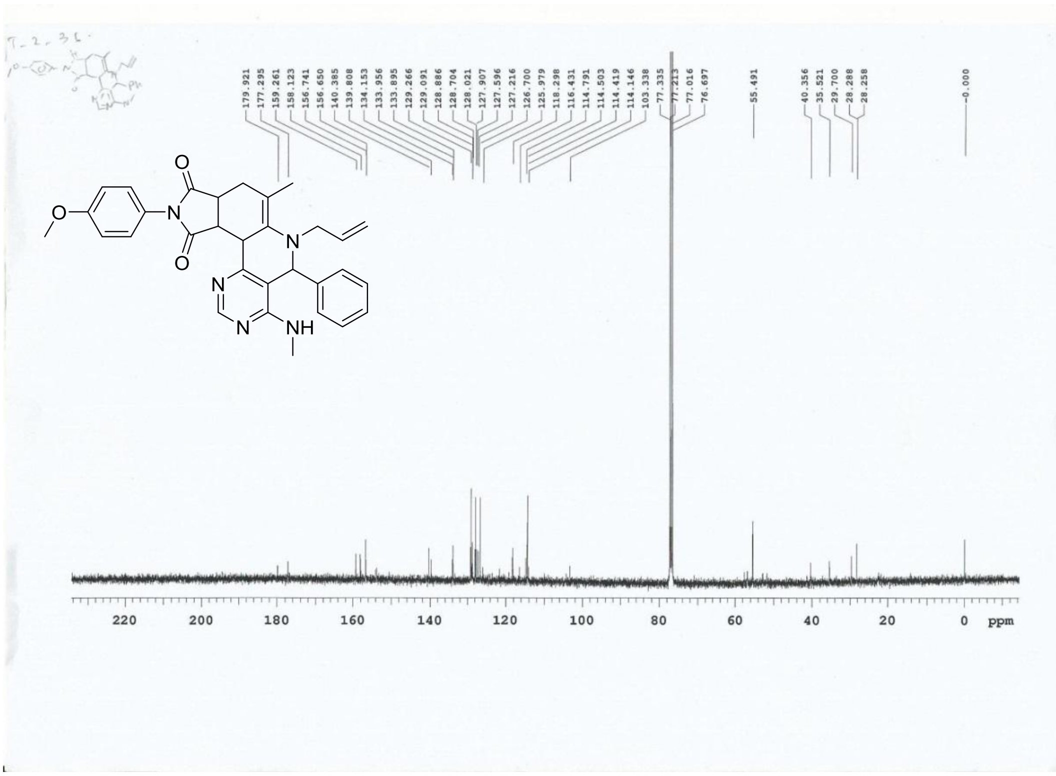
Compound 7d



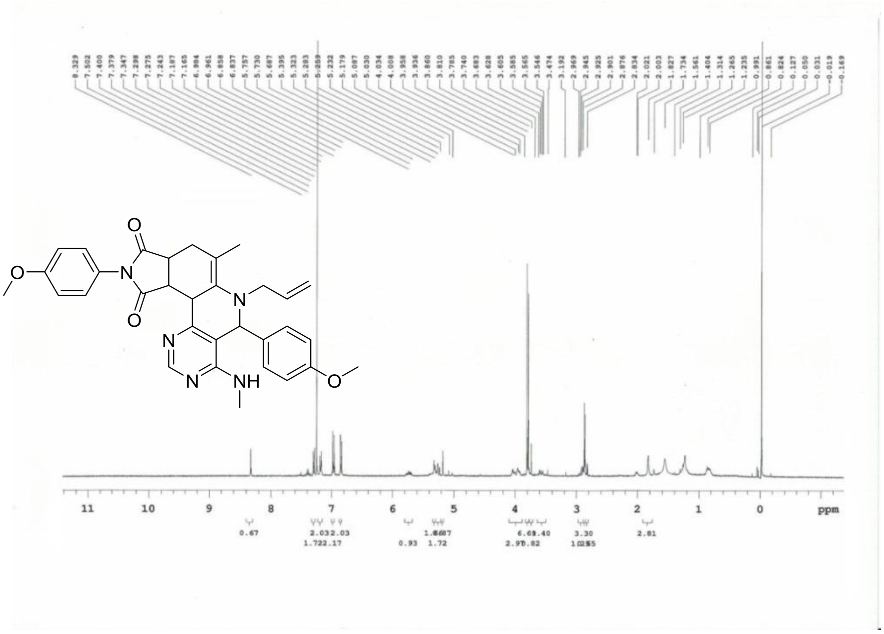


Compound 7e

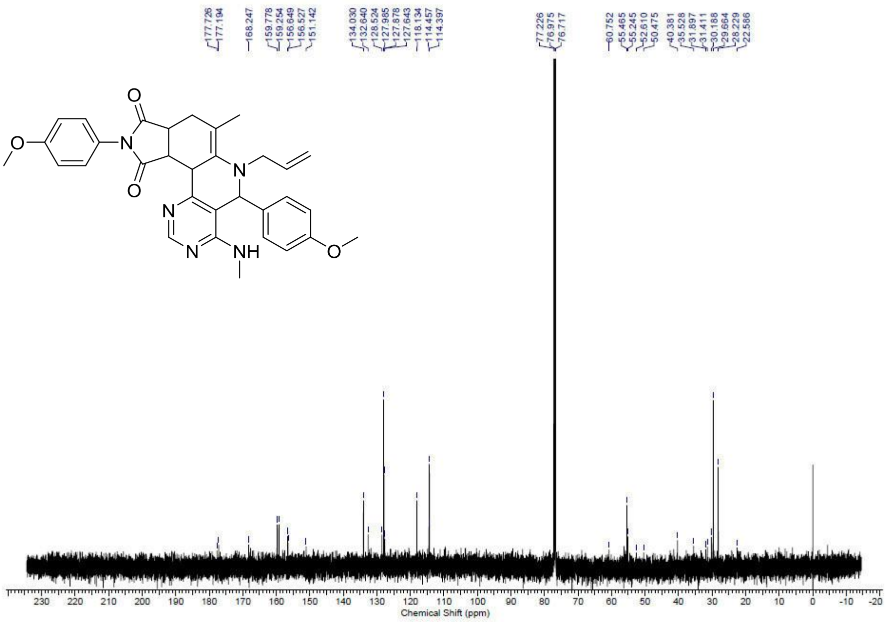




Compound 7f



O
N
O
N
N
N
NH
O
O
ppm

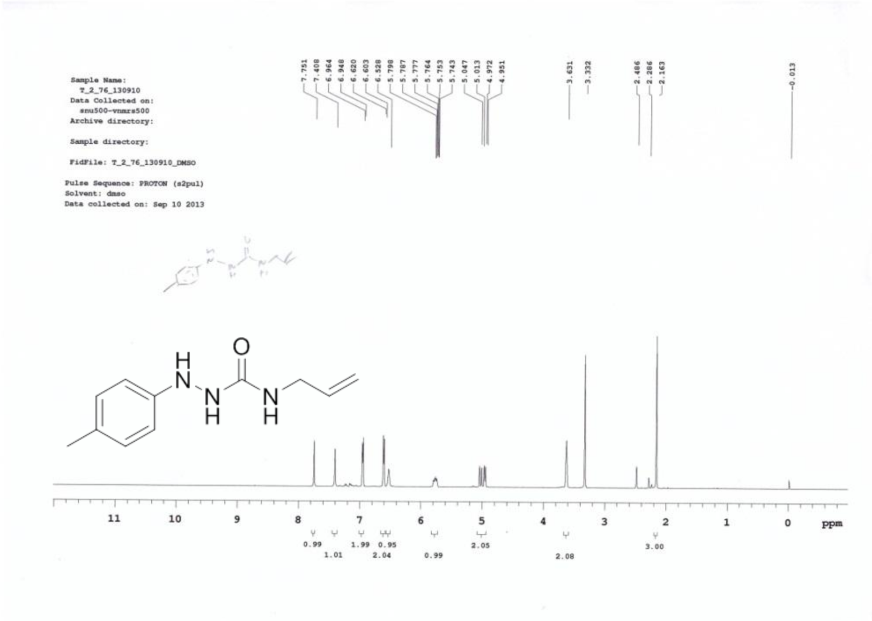


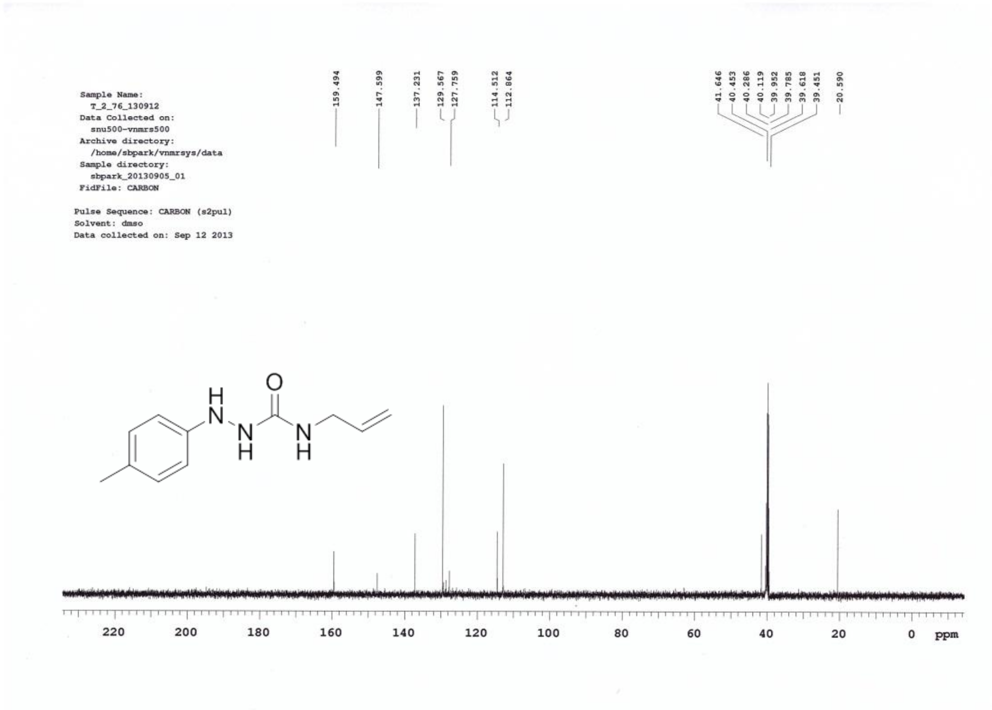
177.726
177.194
168.247
159.778
159.254
158.649
156.527
151.142
134.030
132.640
128.524
127.985
127.878
127.643
118.134
114.457
114.397
77.226
76.975
76.717
60.752
55.465
55.245
52.610
50.475
40.381
35.528
31.897
31.411
30.188
29.664
28.229
22.586
Chemical Shift (ppm)

CHAPTER 2

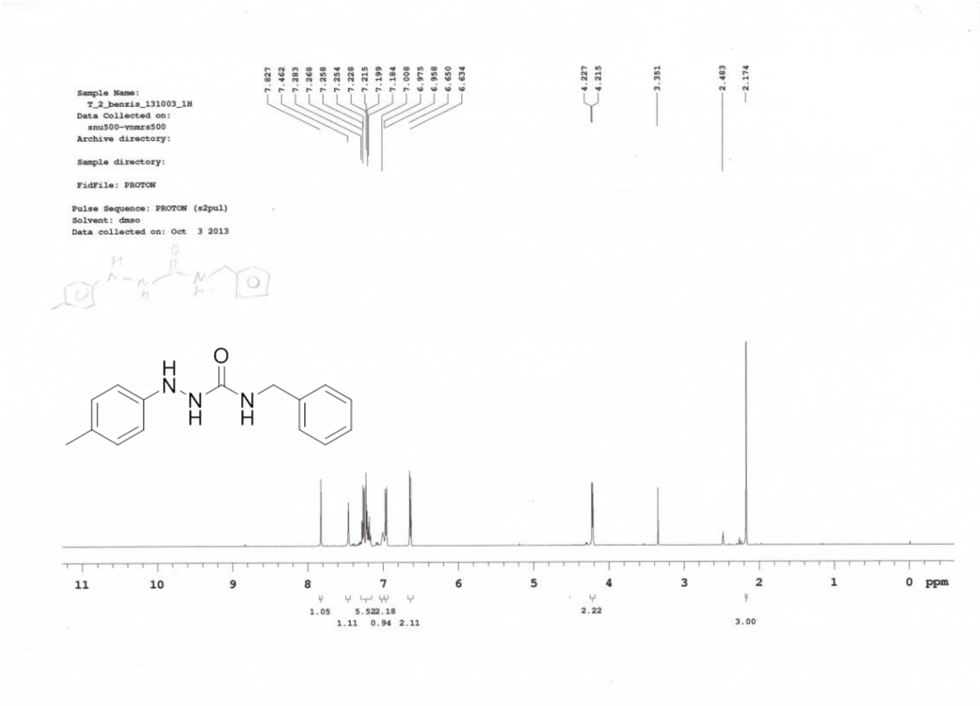
2.1. NMR spectra

Compound 2’a

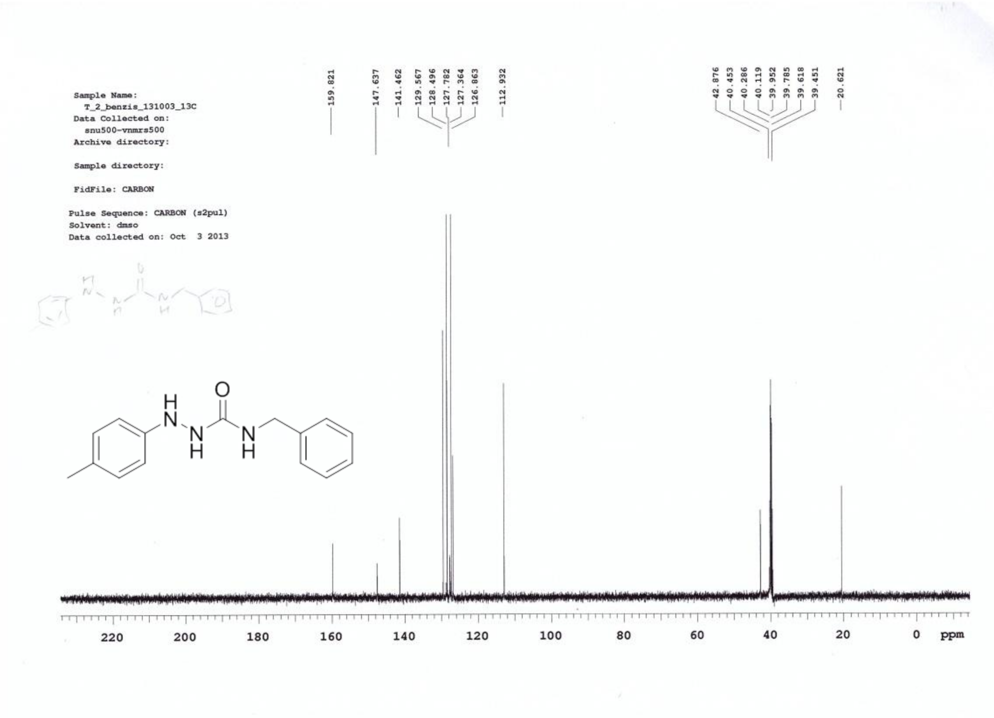




Compound 2’b

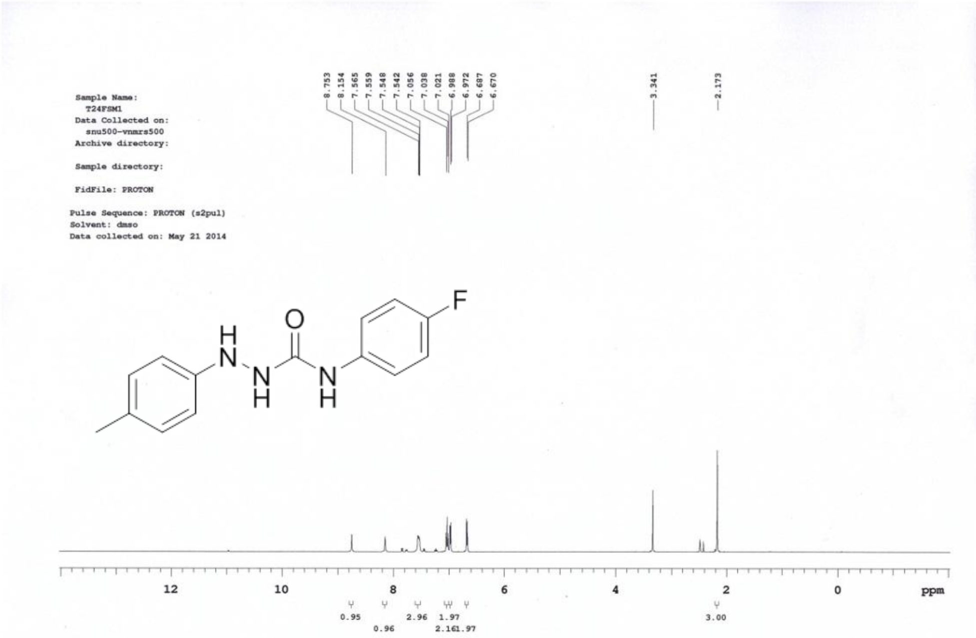


Sample Name:
T_2_benzis_131003_1H
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 3 2013
7.827 7.462 7.283 7.268 7.258 7.254 7.228 7.215 7.199 7.184 7.008 6.975 6.958 6.650 6.634
4.227 4.215
3.351
2.483
2.174
1.05 1.11 5.52 2.18 0.94 2.11
2.22
3.00
ppm

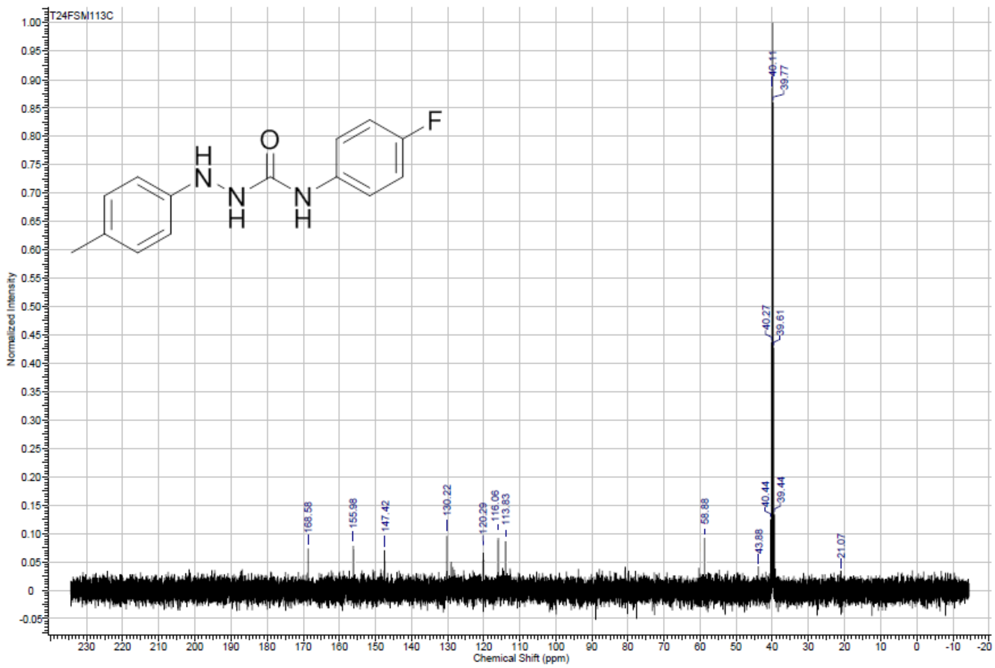


Sample Name:
T_2_benzis_131003_13C
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Oct 3 2013
159.821
147.637
141.462
129.567 128.496 127.782 127.364 126.863
112.932
42.876 40.453 40.286 40.119 39.952 39.785 39.618 39.451
20.621
ppm

Compound 2’c

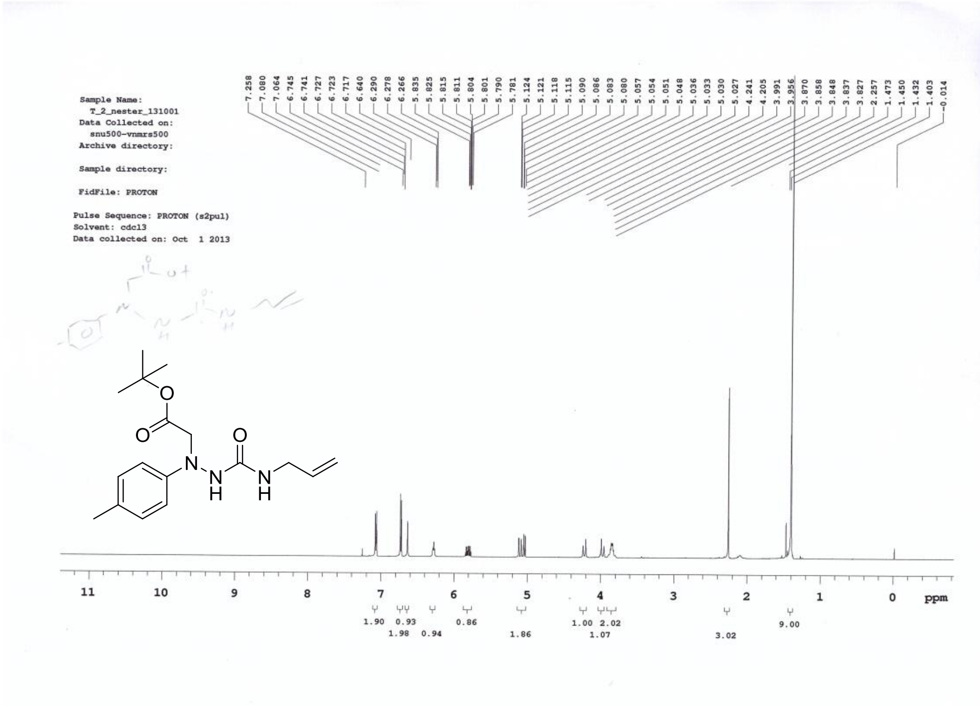


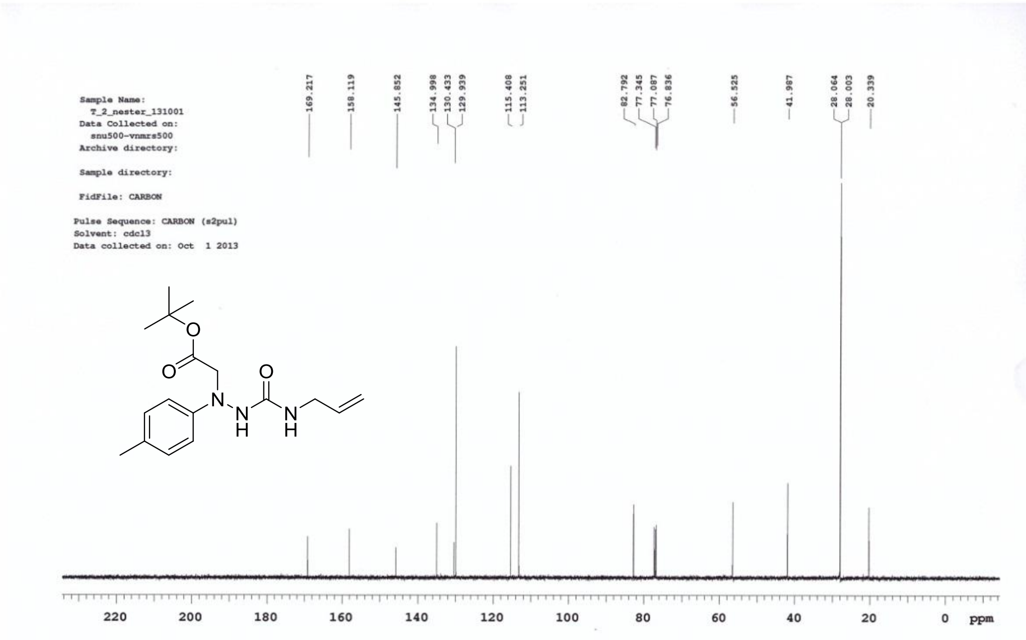
Sample Name:
T24FSM1
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: May 21 2014
8.753
8.154
7.565
7.559
7.548
7.542
7.056
7.038
7.021
6.988
6.972
6.687
6.670
3.341
2.173
F
O
H
N
N
H
N
H
12
10
8
6
4
2
0
ppm
0.95
0.96
2.96
1.97
2.16
1.97
3.00



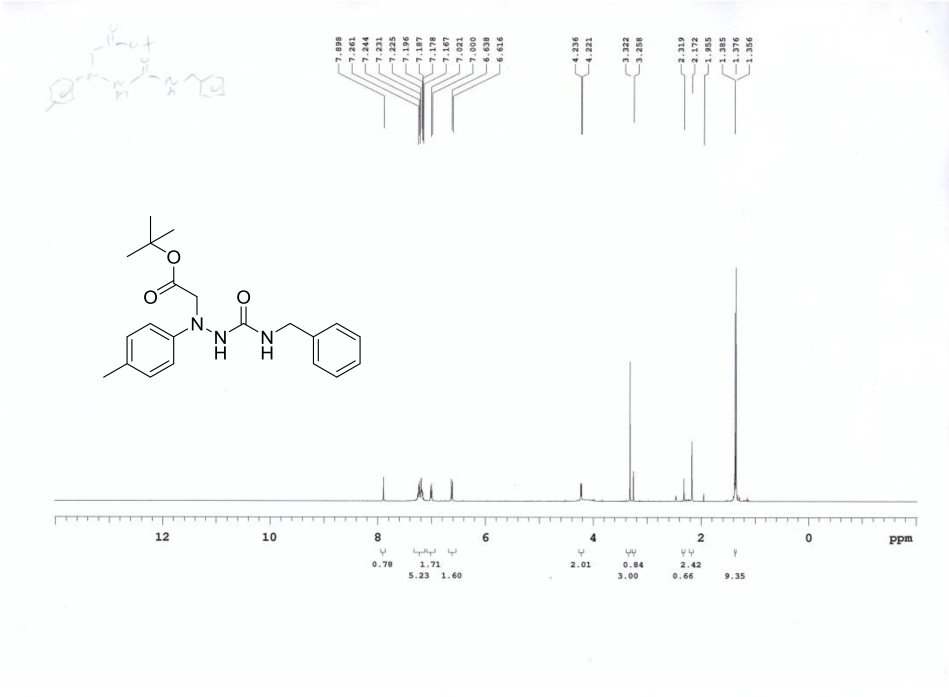
T24FSM113C
40.11
39.77
40.27
39.61
40.44
39.44
168.58
155.98
147.42
130.22
120.29
116.06
113.83
58.88
43.88
21.07
F
O
H
N
N
H
N
H
Normalized Intensity
Chemical Shift (ppm)

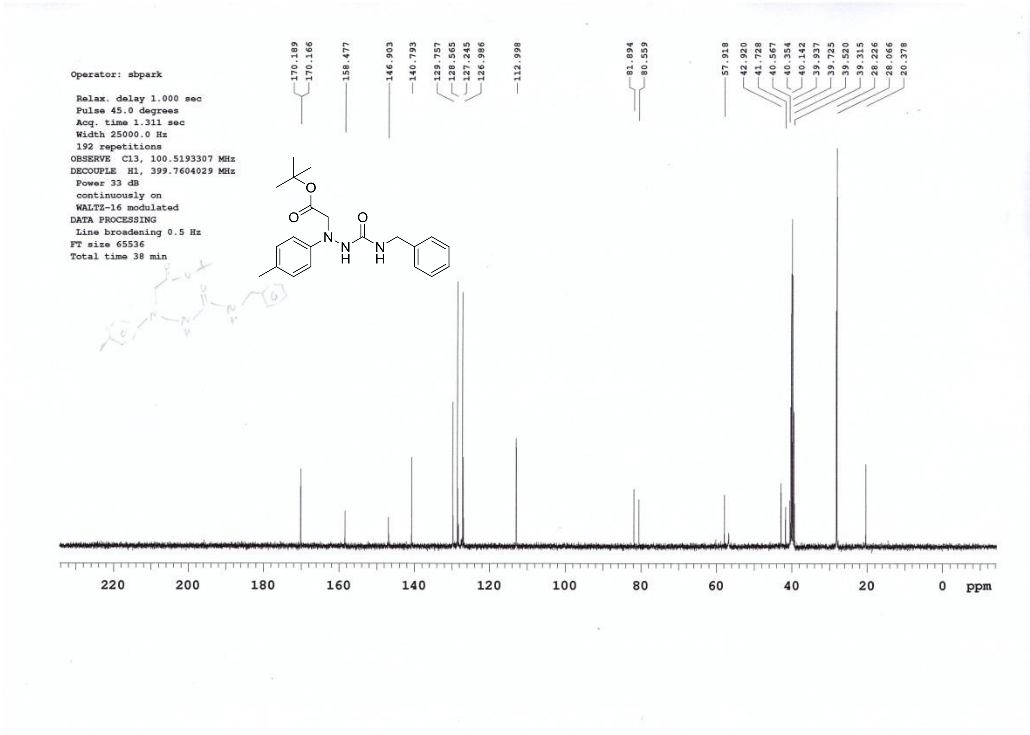
Compound 3’a



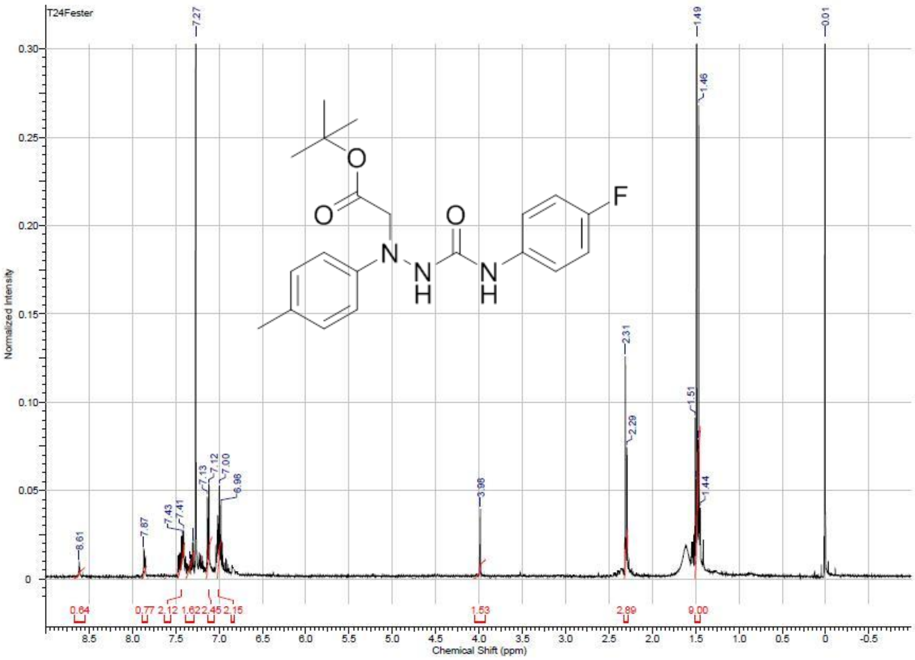


Compound 3’b

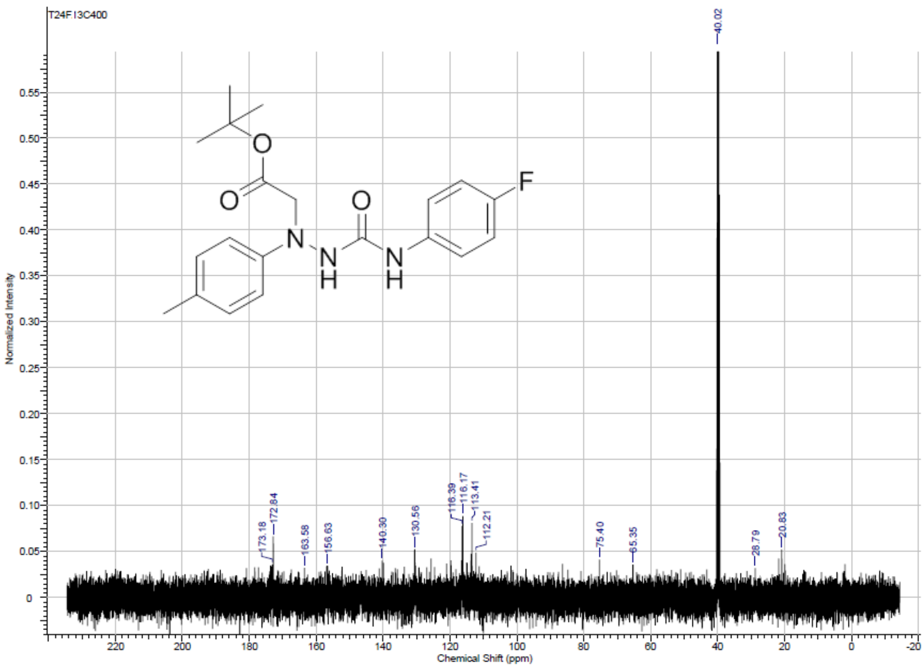



Operator: sbpark
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.311 sec
Width 25000.0 Hz
192 repetitions
OBSERVE C13, 100.5193307 MHz
DECOUPLE H1, 399.7604029 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 38 min

Compound 3'c

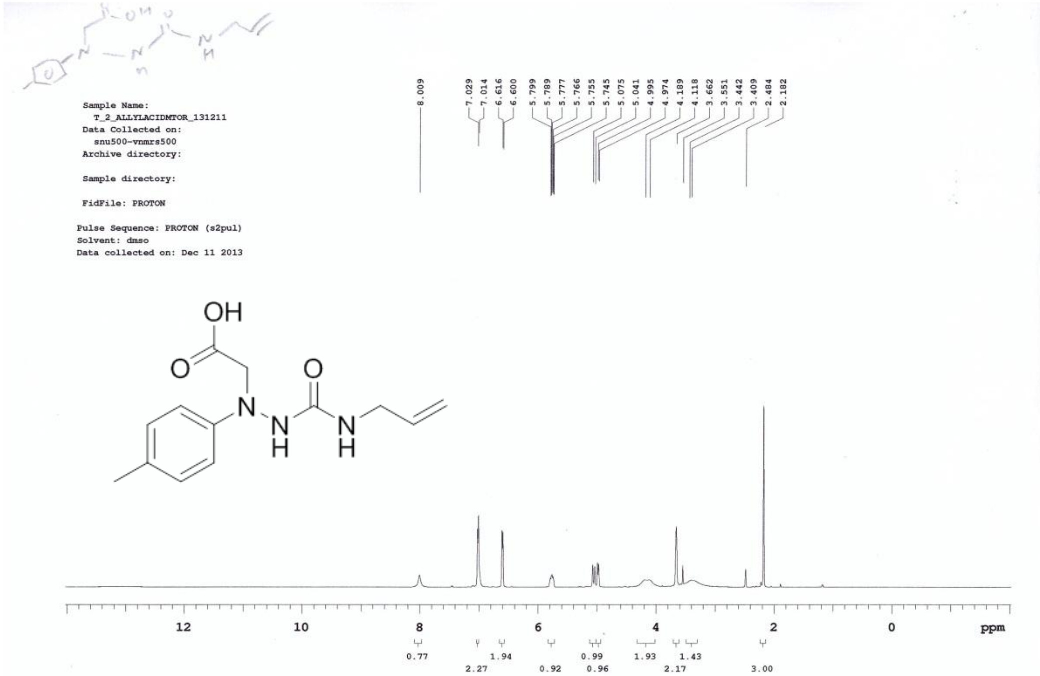


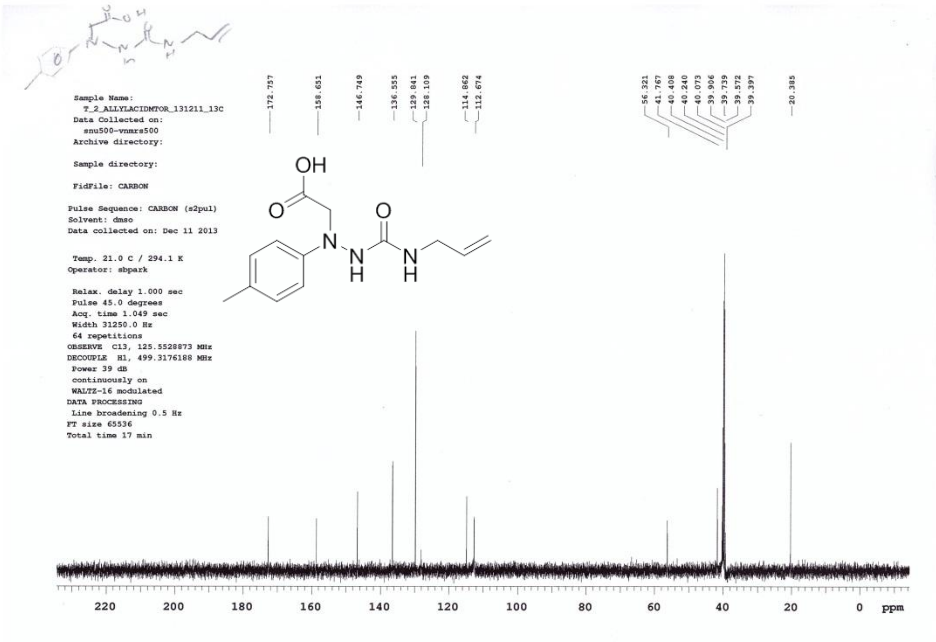
T24Fester
Normalized Intensity
Chemical Shift (ppm)
7.27
1.49
-0.01
1.46
2.31
1.51
2.29
7.13
7.12
7.00
6.98
3.98
7.43
7.41
7.87
8.61
1.44
0.64
0.77
2.12
1.62
2.45
2.15
1.53
2.89
9.00
O
O
O
N
N
H
N
H
F



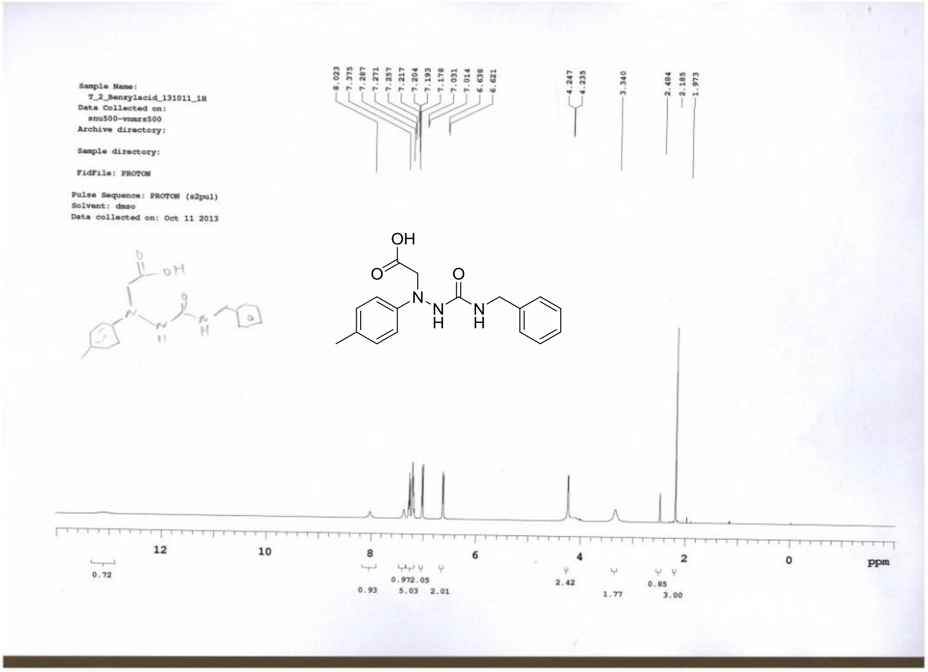
T24F13C400
Normalized Intensity
Chemical Shift (ppm)
40.02
173.18
172.84
163.58
156.63
140.30
130.56
116.39
116.17
113.41
112.21
75.40
65.35
28.79
20.83
O
O
O
N
N
H
N
H
F

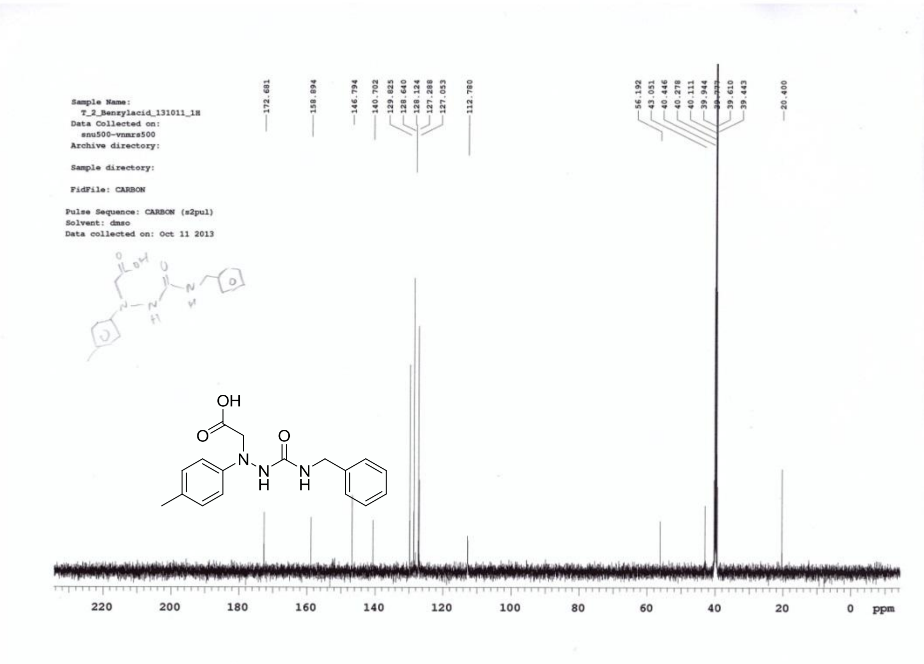
Compound 4’a


Sample Name:
T_2_ALLYLACIDMTOR_131211
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Dec 11 2013
8.009
7.029
7.014
6.616
6.600
5.799
5.789
5.777
5.766
5.755
5.745
5.075
5.041
4.995
4.974
4.189
4.118
3.662
3.551
3.442
3.409
2.484
2.182
0.77
2.27
1.94
0.92
0.99
0.96
1.93
2.17
1.43
3.00
ppm

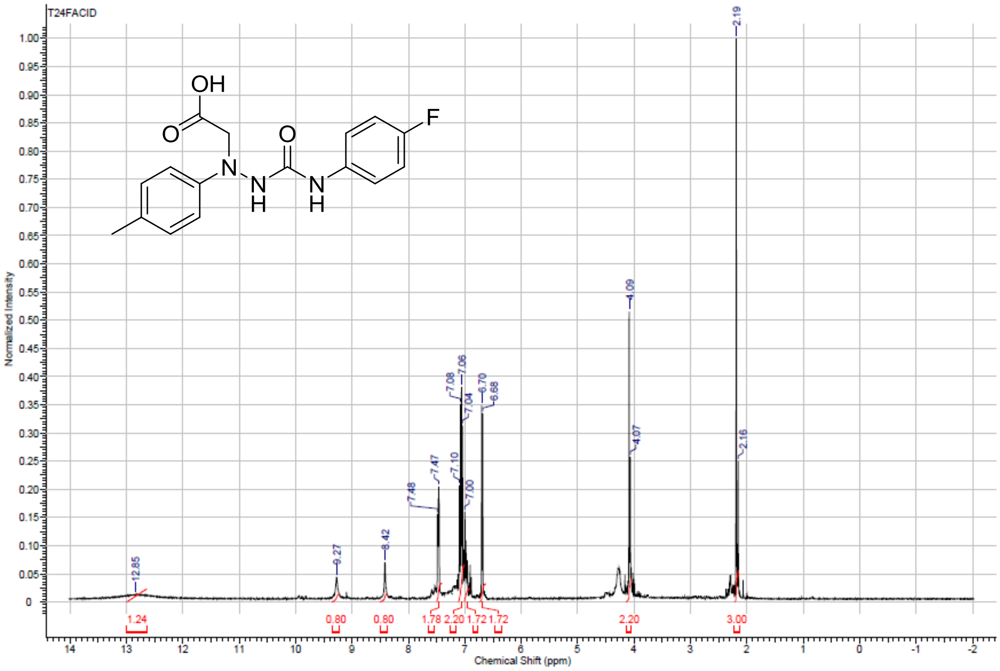

Sample Name:
T_2_ALLYLACIDMTOR_131211_13C
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Dec 11 2013
Temp. 21.0 C / 294.1 K
Operator: sbpark
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.049 sec
Width 31250.0 Hz
64 repetitions
OBSERVE C13, 125.5528873 MHz
DECOUPLE H1, 499.3176188 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 17 min
172.757
158.651
146.749
136.555
129.841
128.109
114.862
112.674
56.321
41.767
40.408
40.240
40.073
39.906
39.739
39.572
39.397
20.385
ppm

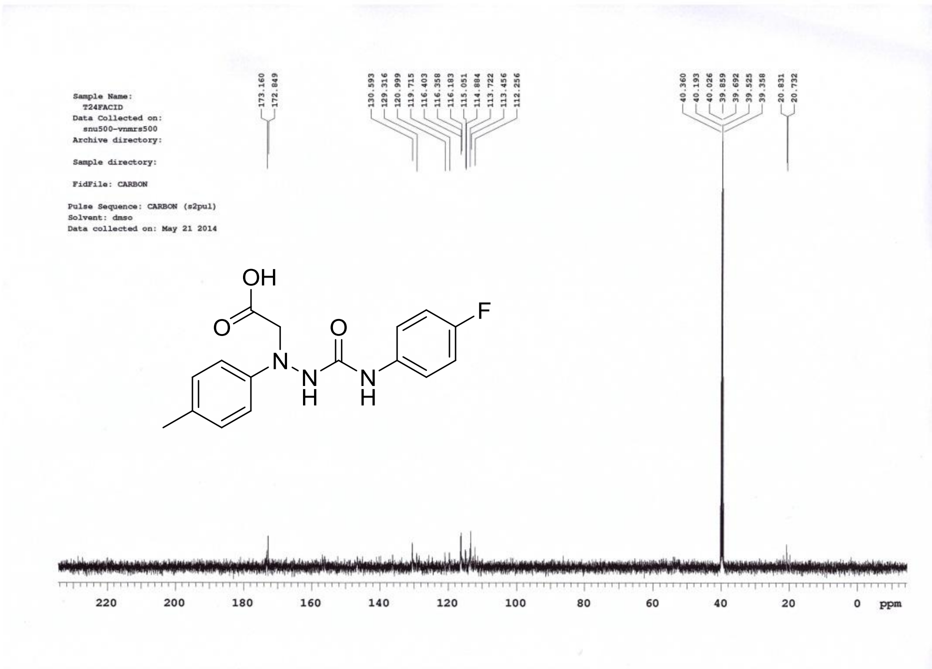
Compound 4’b


Sample Name:
T_2_Benzylacid_131011_1H
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: PROTON
Pulse Sequence: PROTON (s2pul)
Solvent: dmso
Data collected on: Oct 11 2013
8.023 7.375 7.287 7.271 7.257 7.217 7.204 7.193 7.178 7.031 7.014 6.638 6.621
4.247 4.235
3.340
2.484 2.185 1.973
OH
O
O
N
N
H
N
H
ppm
0.72 0.93 0.97 2.05 5.03 2.01 2.42 1.77 0.85 3.00


Sample Name:
T_2_Benzylacid_131011_1H
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: Oct 11 2013
172.681
158.894
146.794 140.702 129.825 128.640 128.124 127.288 127.053
112.780
56.192 43.051 40.446 40.278 40.111 39.944 39.610 39.443
20.400
ppm

Compound 4’c

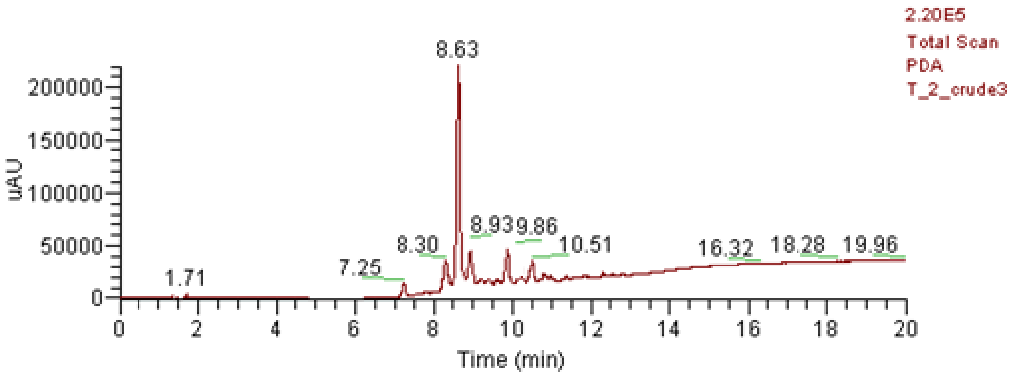

T24FACID
Normalized Intensity
Chemical Shift (ppm)
12.85
9.27
8.42
7.48
7.47
7.10
7.08
7.06
7.04
7.00
6.70
6.68
4.09
4.07
2.19
2.16
1.24
0.80
0.80
1.78
2.20
1.72
1.72
2.20
3.00
OH
O
O
N
N
H
N
H
F


Sample Name:
T24FACID
Data Collected on:
snu500-vnmrs500
Archive directory:
Sample directory:
FidFile: CARBON
Pulse Sequence: CARBON (s2pul)
Solvent: dmso
Data collected on: May 21 2014
173.160
172.849
130.593
129.316
120.999
119.715
116.403
116.358
116.183
115.051
114.884
113.722
113.456
112.256
40.360
40.193
40.026
39.859
39.692
39.525
39.358
20.831
20.732
ppm
OH
O
O
N
N
H
N
H
F

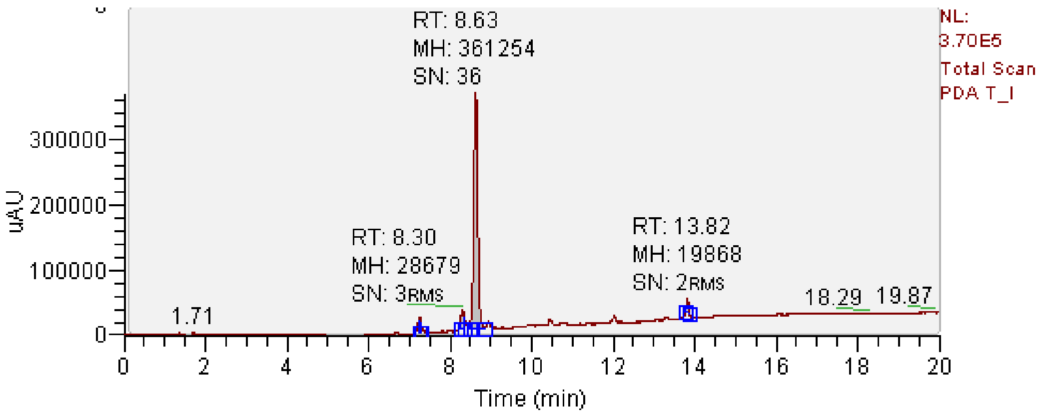
2.2. 1H/13C-NMR and PDA based LC/MS data for representative compounds

2.2.1Compound 10{a,2,9}

Crude LC

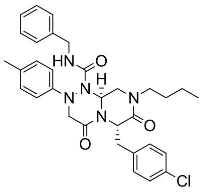


LC after fast purify

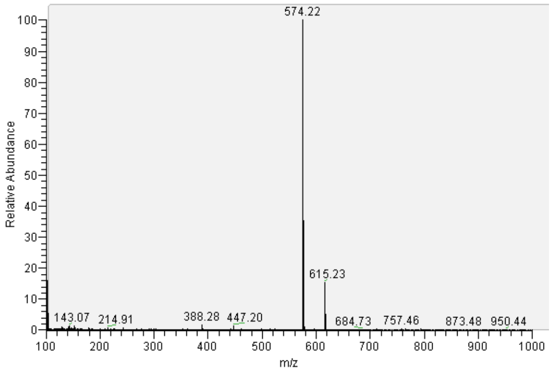


PEAK LIST
T_P9.RAW
RT: 0.00 - 20.00
Number of detected peaks: 4

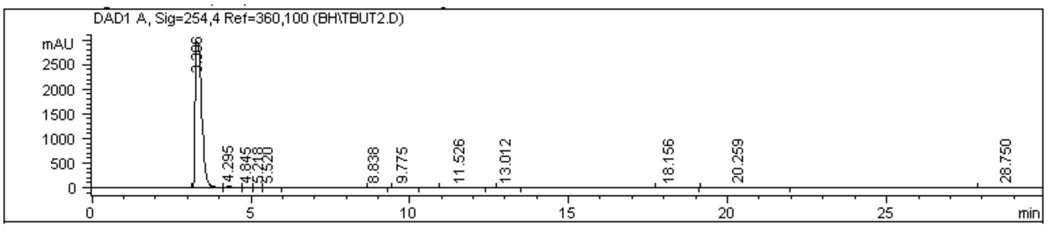
Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.26	7.22	7.28	79896.75	2.93	24412	5.62
8.3	8.24	8.34	126658	4.63	28678.89	6.6
8.63	8.48	8.84	2462377	90.11	361253.9	83.2
13.82	13.79	13.87	63653.27	2.33	19867.67	4.58



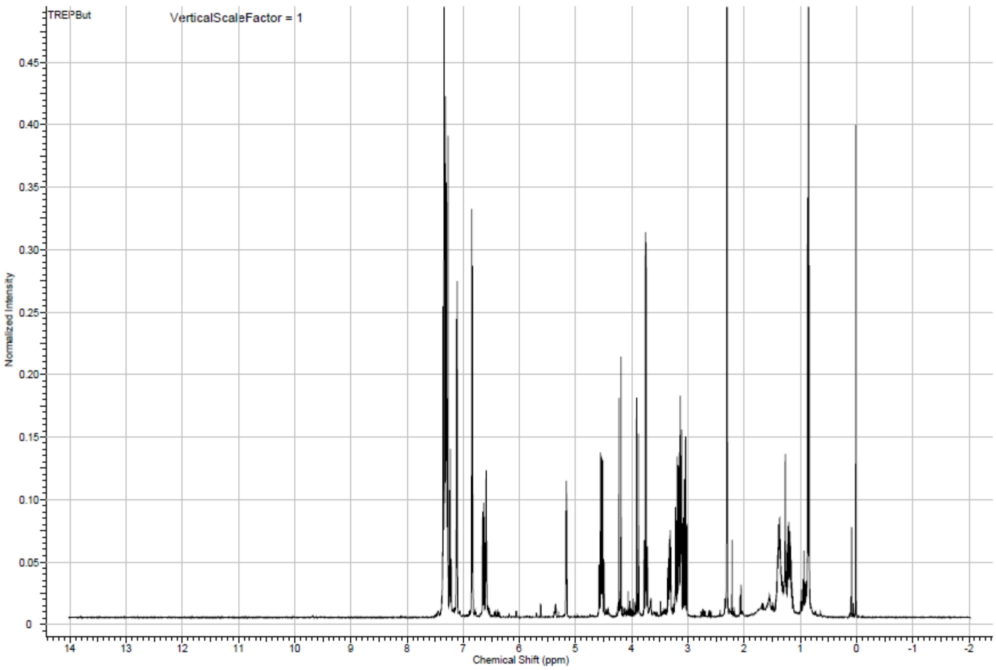
Exact Mass: 573.25
Molecular Weight: 574.11



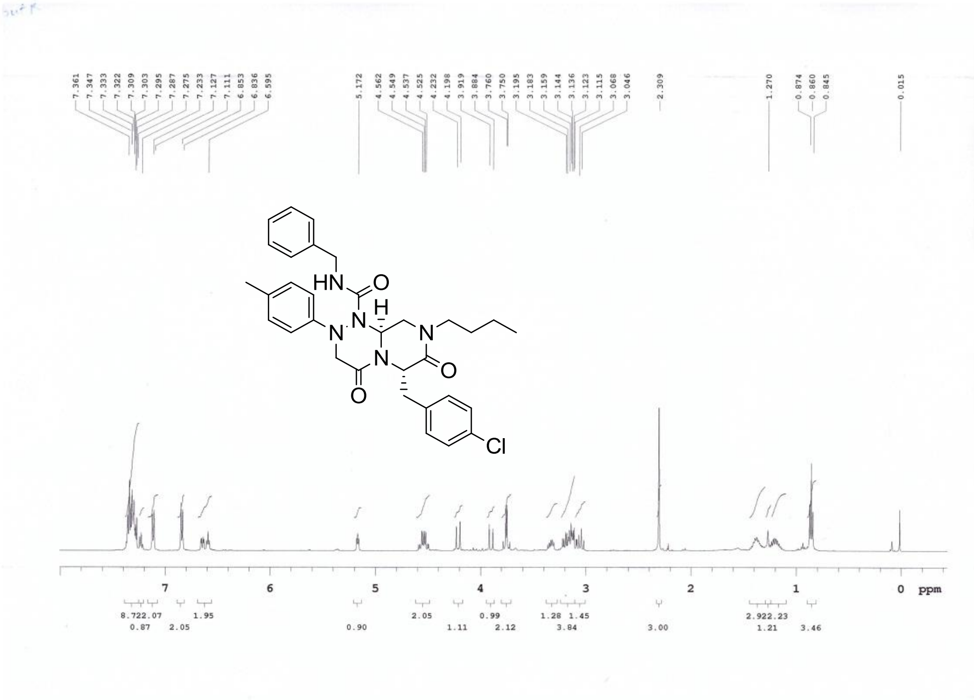
Chiral HPLC

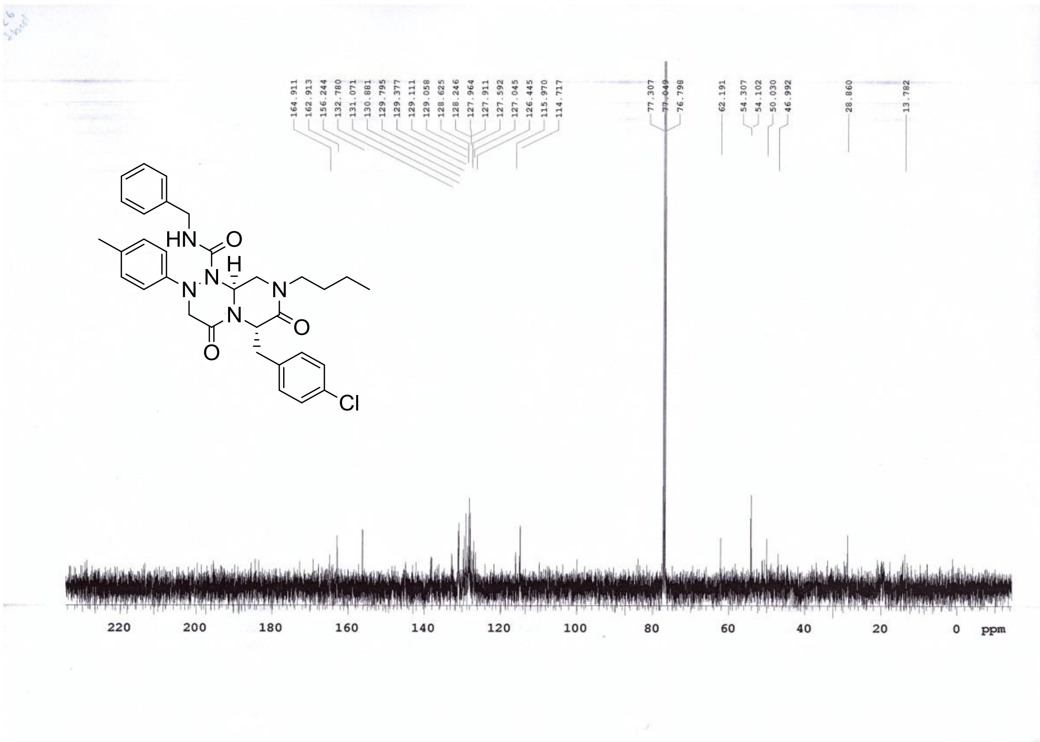


Crude 1HNMR

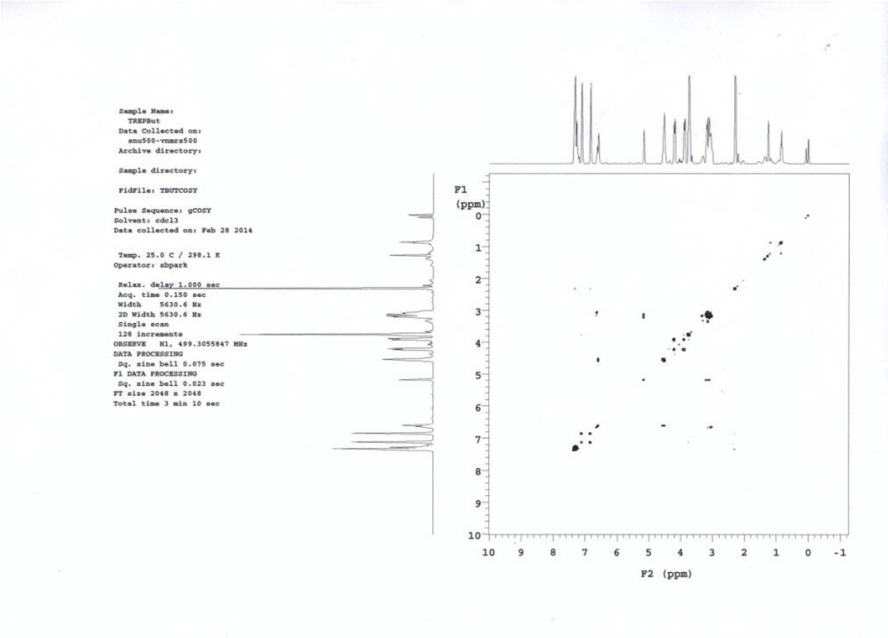


1H NMR and 13C

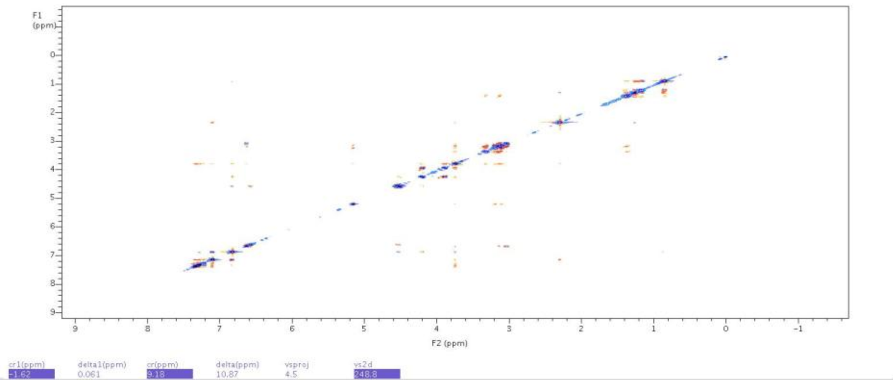


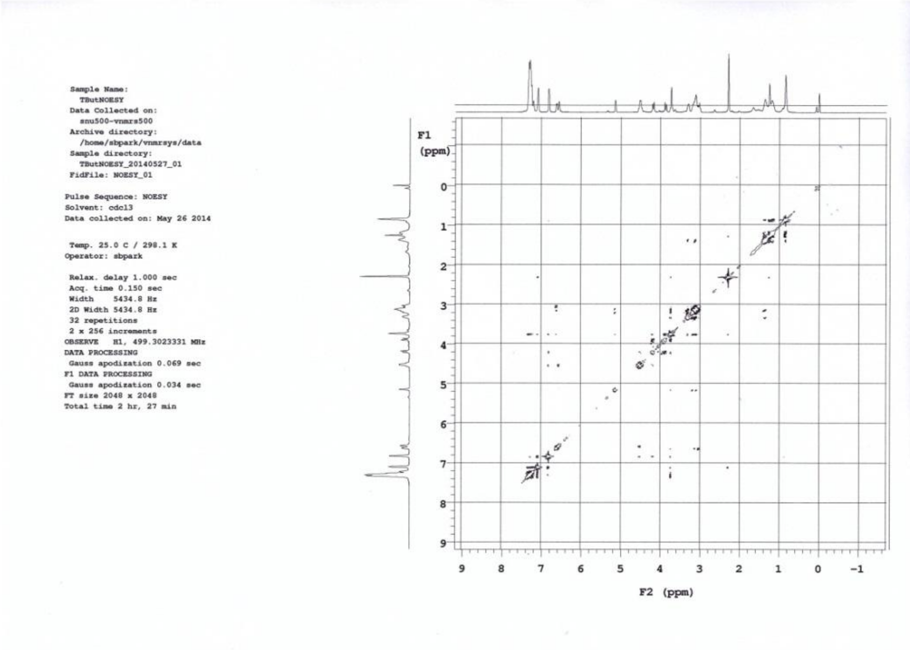


COSY



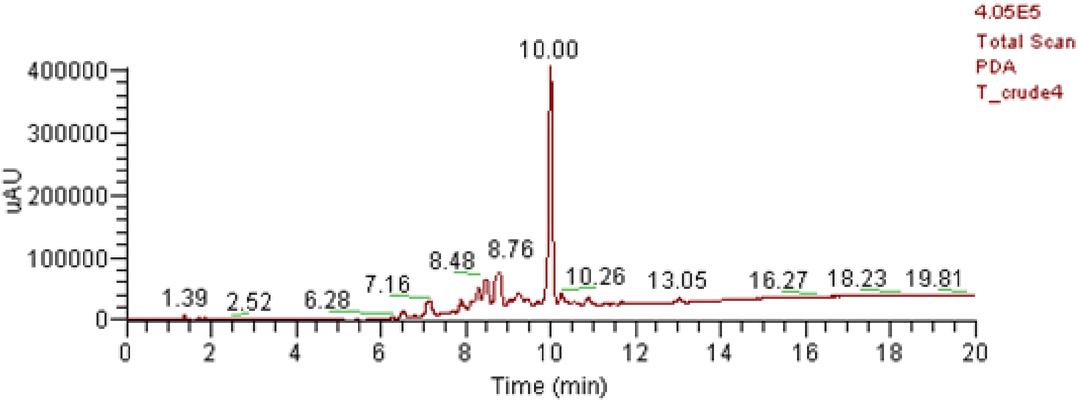
2D NOESY



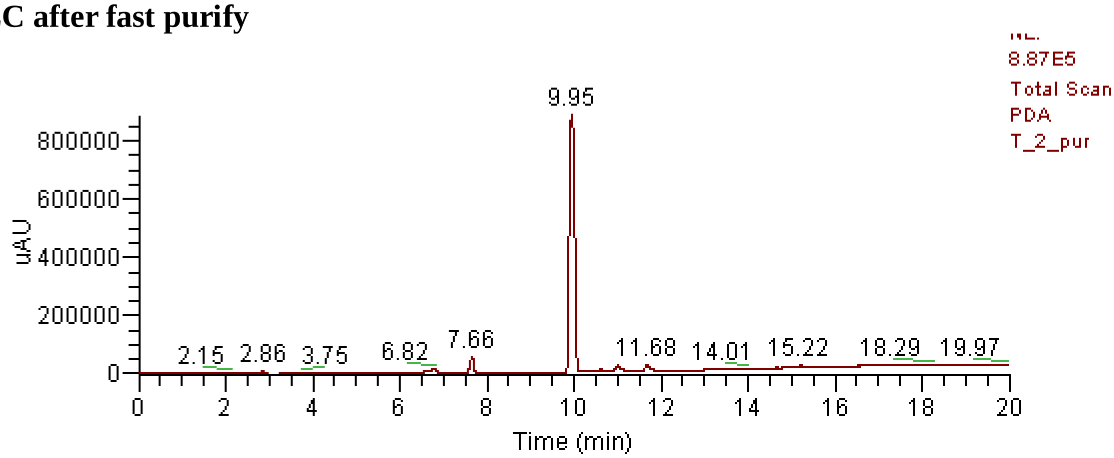

Sample Name:
TButNOESY
Data Collected on:
snu500-vnmrs500
Archive directory:
/home/sbpark/vnmrsys/data
Sample directory:
TButNOESY_20140527_01
FidFile: NOESY_01
Pulse Sequence: NOESY
Solvent: cdcl3
Data collected on: May 26 2014
Temp. 25.0 C / 298.1 K
Operator: sbpark
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 5434.8 Hz
2D Width 5434.8 Hz
32 repetitions
2 x 256 increments
OBSERVE H1, 499.3023331 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.034 sec
FT size 2048 x 2048
Total time 2 hr, 27 min
F1 (ppm)
F2 (ppm)

2.2.2.Compound 10{b,3,4}

Crude LC

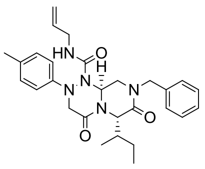


LC after fast purify

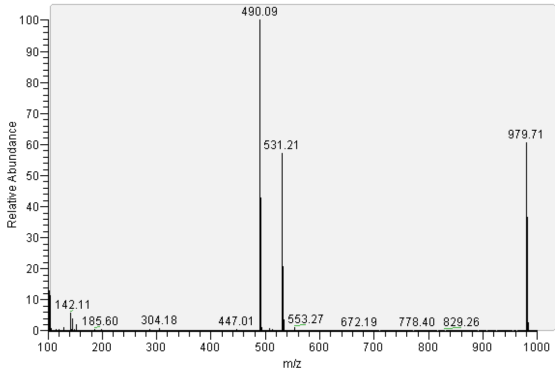


PEAK LIST
TX4.RAW
RT: 0.00 - 20.00
Number of detected peaks: 2

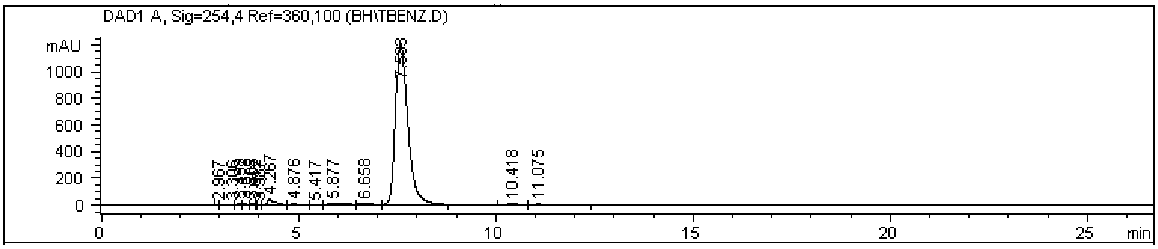
Apex RT	Start RT	End RT	Area	%Area	Height	%Height
7.66	7.6	7.7	273548.8	3.52	59534.75	6.29
9.95	9.83	10.15	7488185	96.48	886687.7	93.71



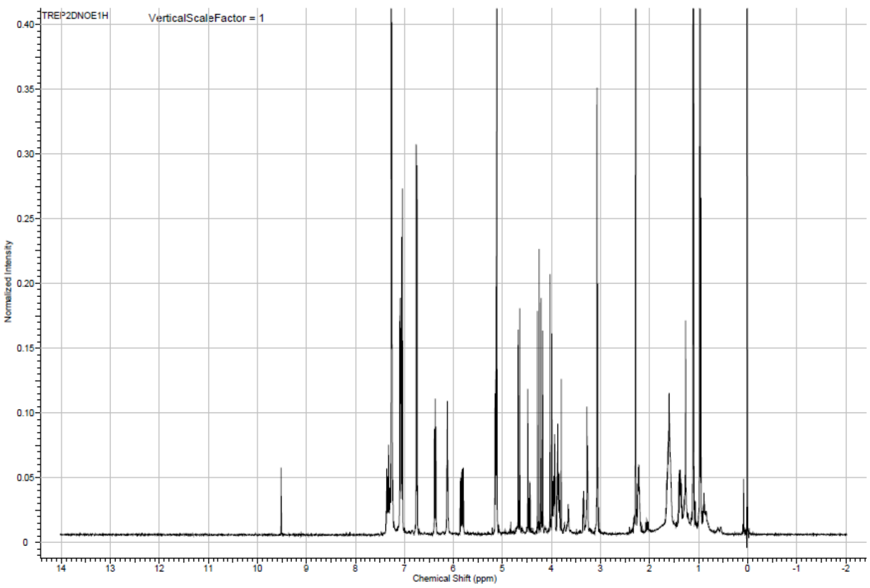
Exact Mass: 489.27
Molecular Weight: 489.61



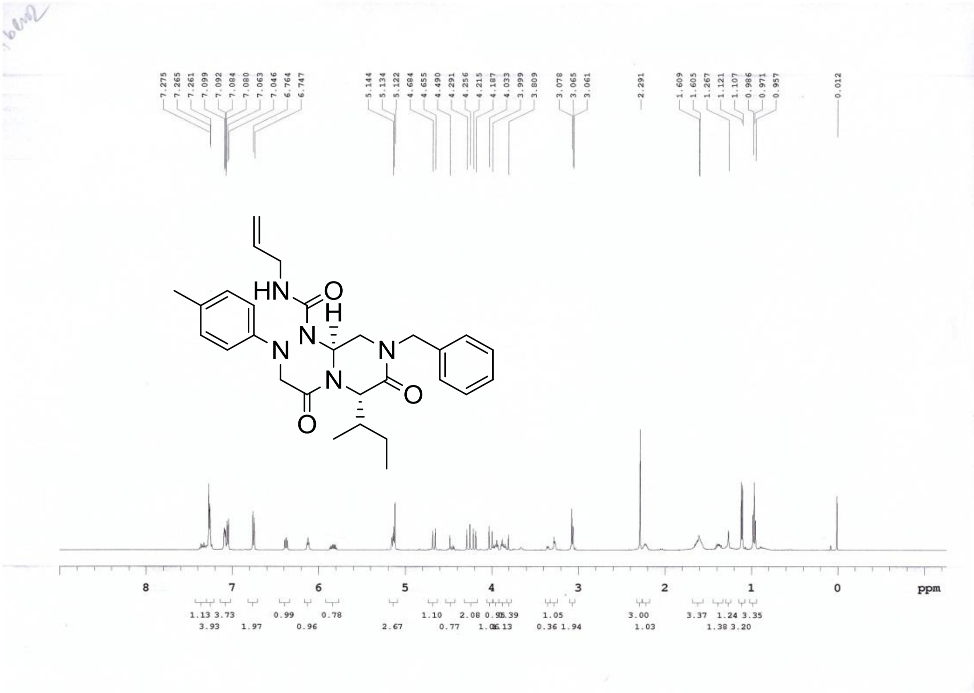
Chiral HPLC

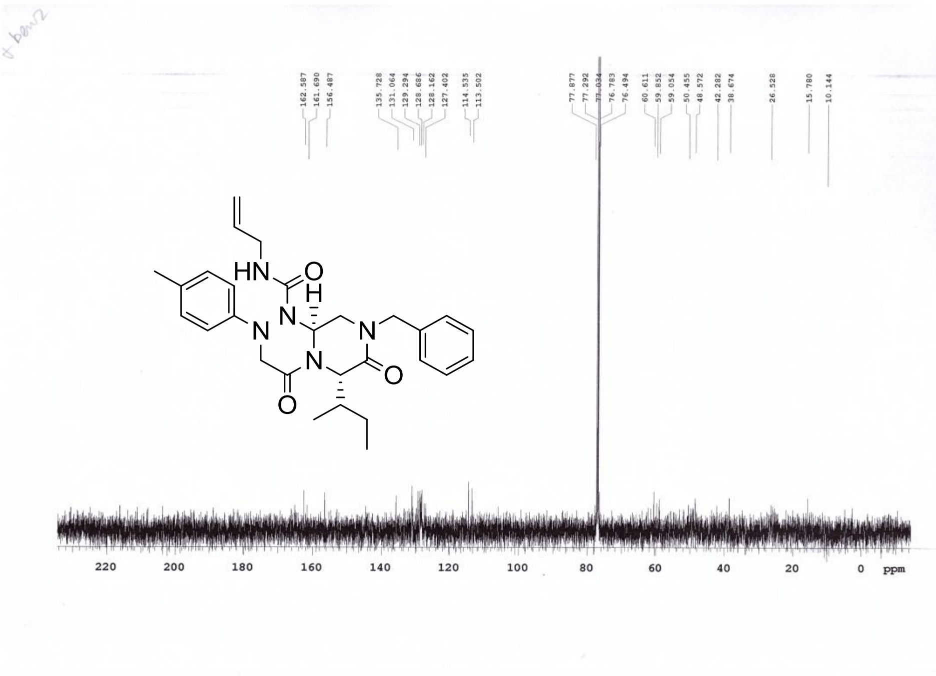


Crude 1H NMR

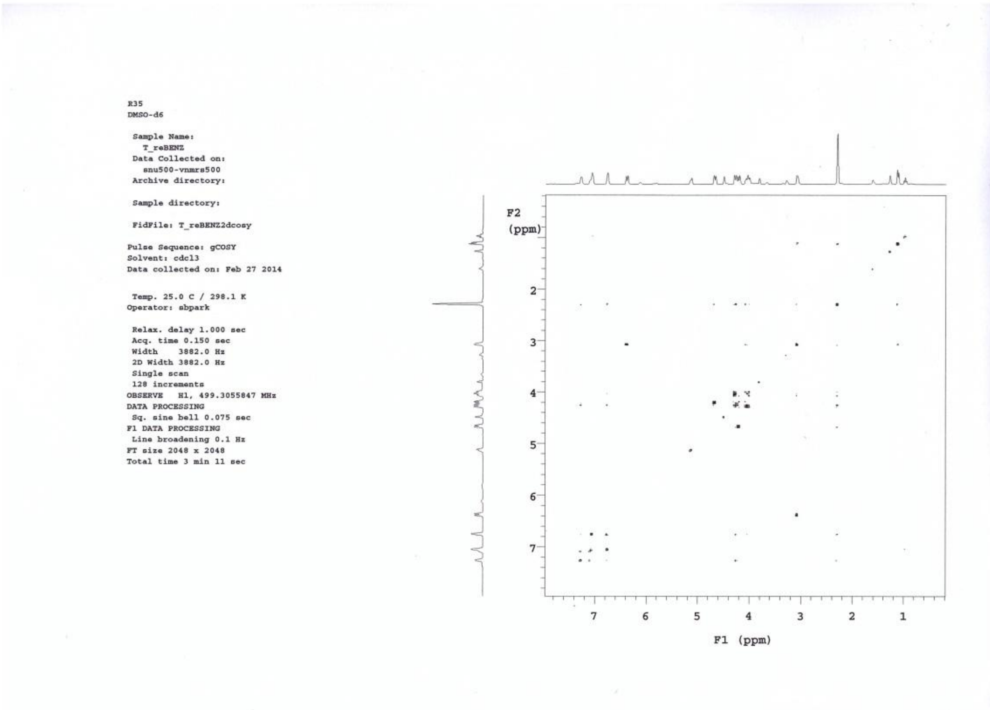


1H and 13 C NMR

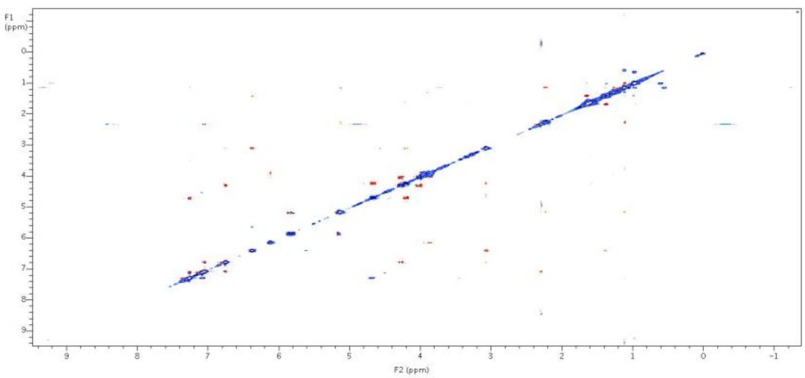


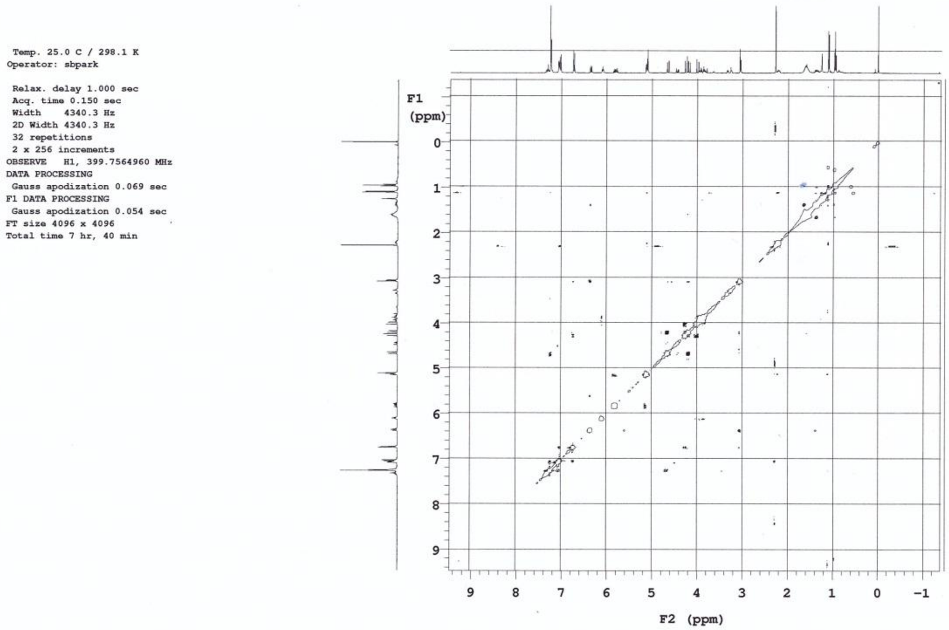


COSY

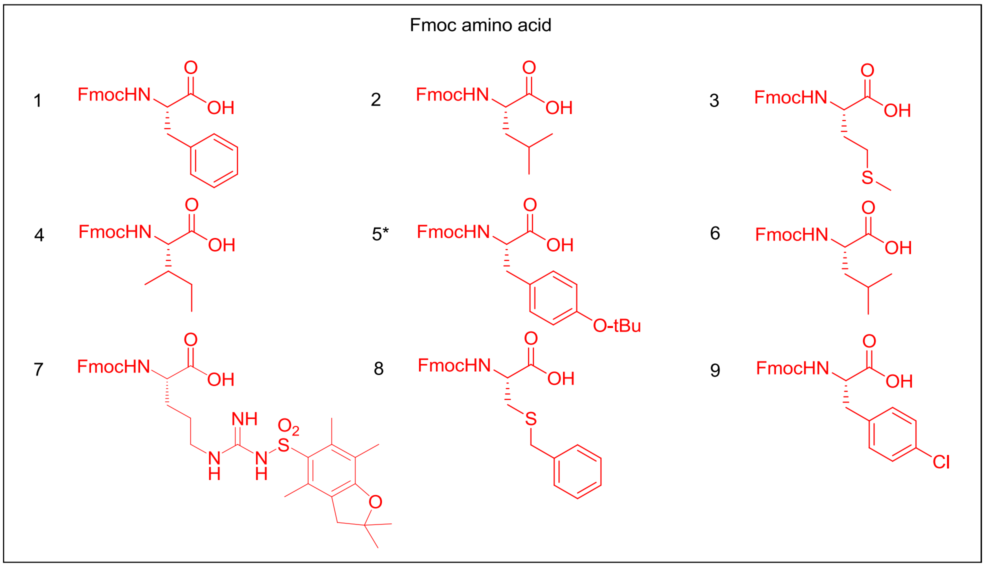


2D NOESY

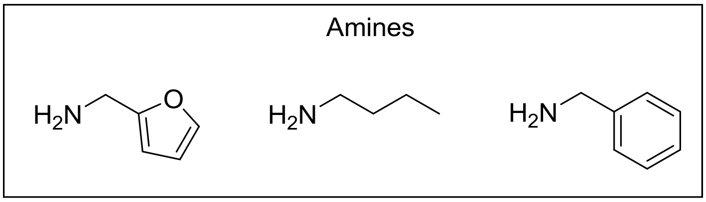



Temp. 25.0 C / 298.1 K
Operator: sbpark
Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 4340.3 Hz
2D Width 4340.3 Hz
32 repetitions
2 x 256 increments
OBSERVE H1, 399.7564960 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.054 sec
FT size 4096 x 4096
Total time 7 hr, 40 min
F1 (ppm)
F2 (ppm)

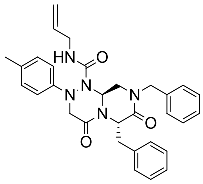
2.3. List of nine Fmoc Amino acids (R_4) and three amines (R_3) used for library construction



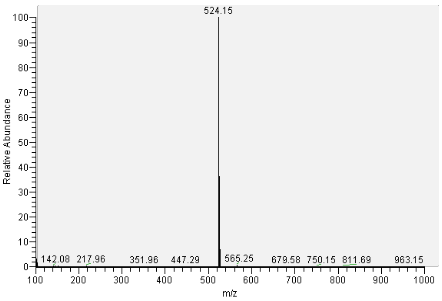
Note: 5*OH-free after cleavage from the resin

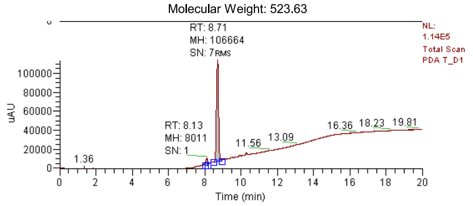


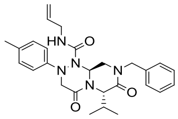
2.4. PDA based LC/MS analysis data for library compounds



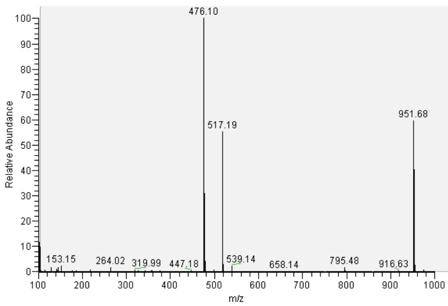
Exact Mass: 523.26
Molecular Weight: 523.63

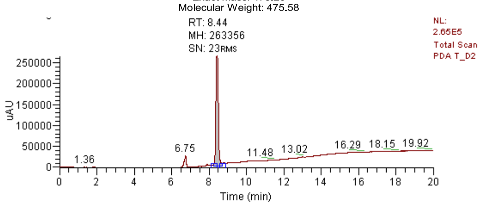


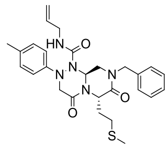




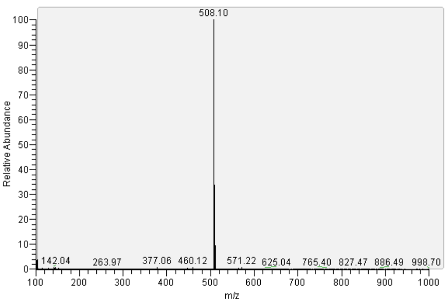
Exact Mass: 475.26
Molecular Weight: 475.58

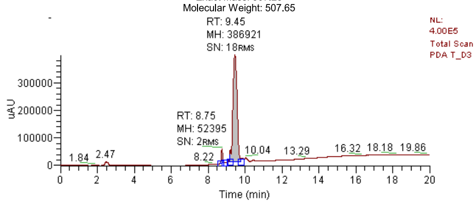


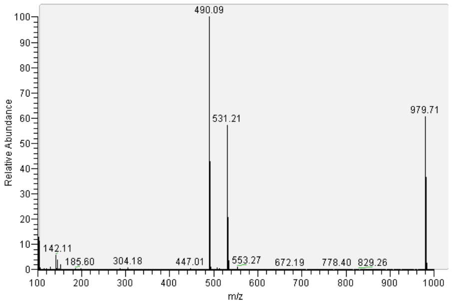


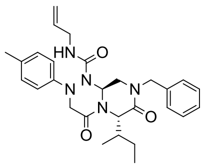


Exact Mass: 507.23
Molecular Weight: 507.65

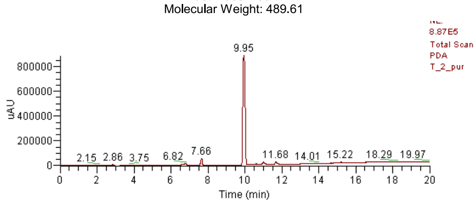


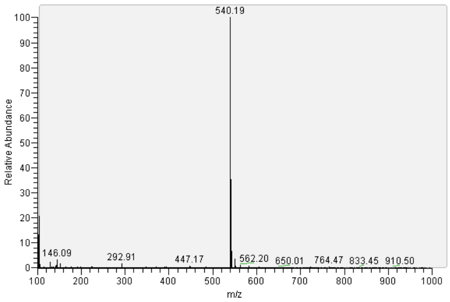


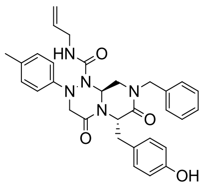




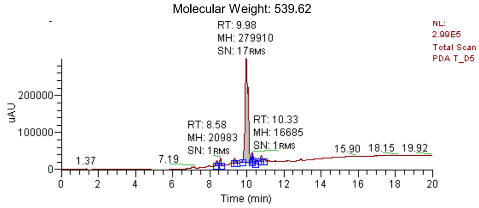
Exact Mass: 489.27
Molecular Weight: 489.61

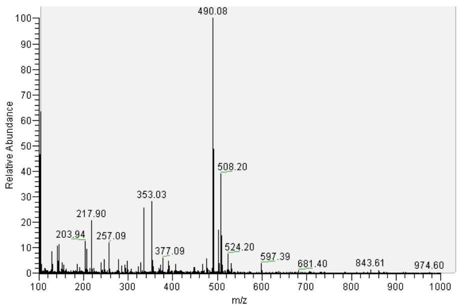


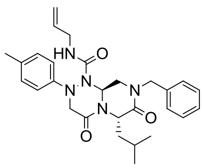




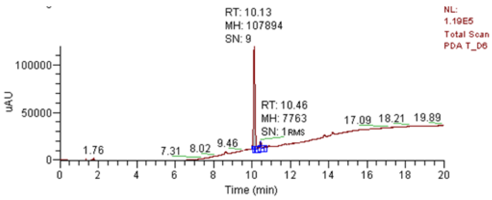
Exact Mass: 539.25
Molecular Weight: 539.62

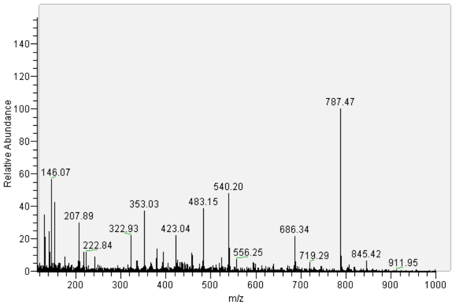


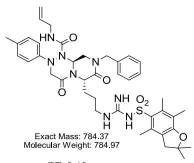


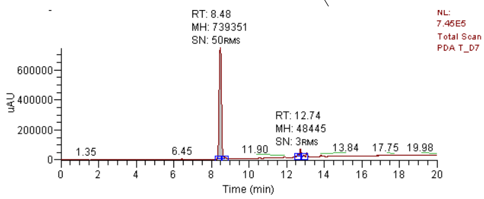


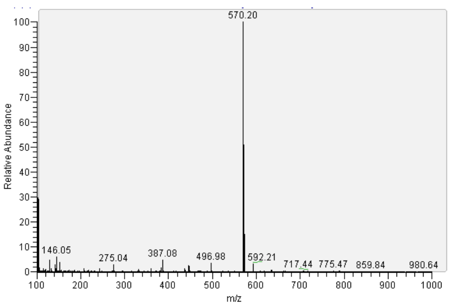
Exact Mass: 489.27
Molecular Weight: 489.61

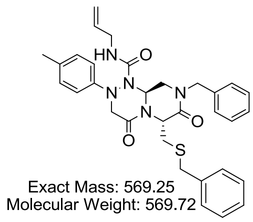


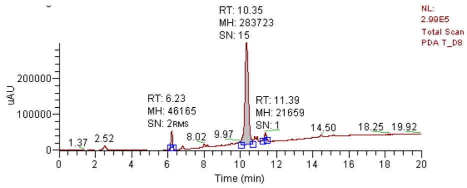

787.47
540.20
483.15
353.03
146.07
207.89
322.93
423.04
686.34
222.84
556.25
719.29
845.42
911.95
Relative Abundance
m/z

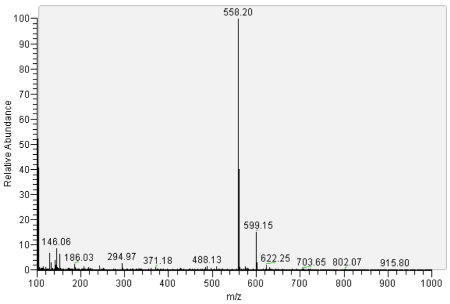

Exact Mass: 784.37
Molecular Weight: 784.97

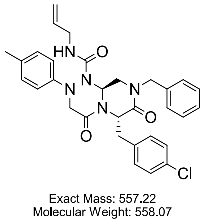

RT: 8.48
MH: 739351
SN: 50RMS
NL:
7.45E5
Total Scan
PDA T_D7
RT: 12.74
MH: 48445
SN: 3RMS
1.35
6.45
11.90
13.84
17.75
19.98
uAU
Time (min)

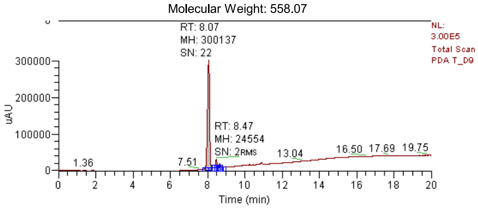

570.20
146.05
275.04
387.08
496.98
592.21
717.44
775.47
859.84
980.64
Relative Abundance
m/z

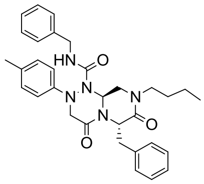

Exact Mass: 569.25
Molecular Weight: 569.72


RT: 10.35
MH: 283723
SN: 15
NL:
2.99E5
Total Scan
PDA T_D8
RT: 6.23
MH: 46165
SN: 2RMS
RT: 11.39
MH: 21659
SN: 1
1.37
2.52
8.02
9.97
14.50
18.25
19.92
uAU
Time (min)

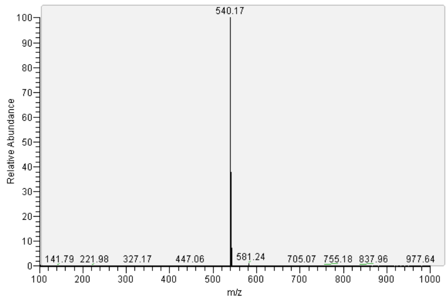

558.20
599.15
146.06
186.03
294.97
371.18
488.13
622.25
703.65
802.07
915.80
Relative Abundance
m/z

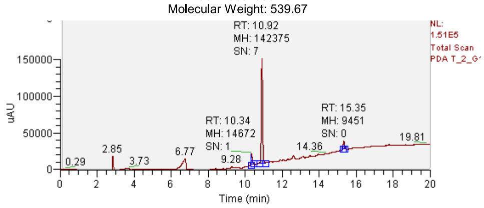

Exact Mass: 557.22
Molecular Weight: 558.07

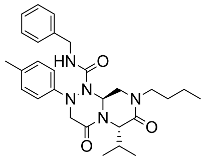

RT: 8.07
MH: 300137
SN: 22
NL:
3.00E5
Total Scan
PDA T_D9
RT: 8.47
MH: 24554
SN: 2RMS
1.36
7.51
13.04
16.50
17.69
19.75
uAU
Time (min)



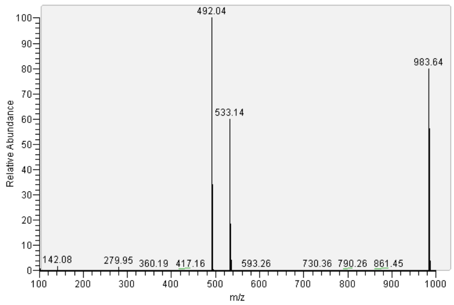
Exact Mass: 539.29
Molecular Weight: 539.67

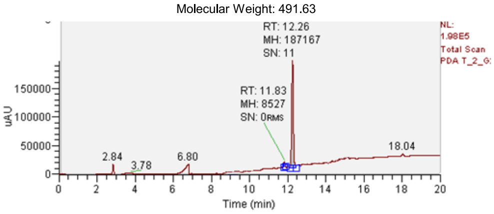


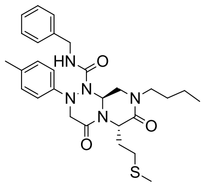




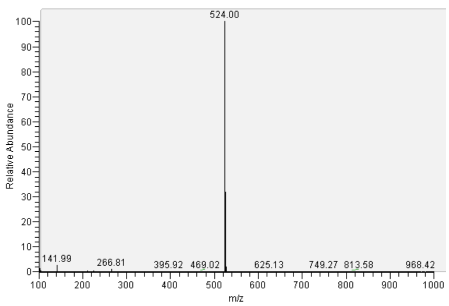
Exact Mass: 491.29
Molecular Weight: 491.63

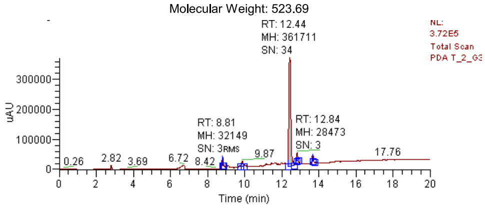


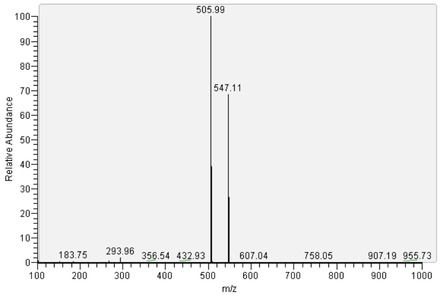


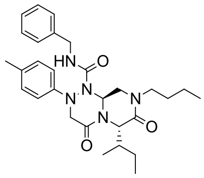


Exact Mass: 523.26
Molecular Weight: 523.69

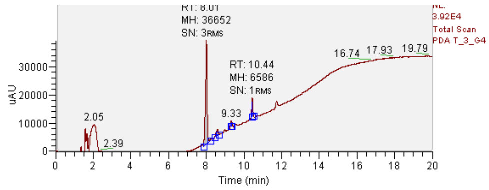


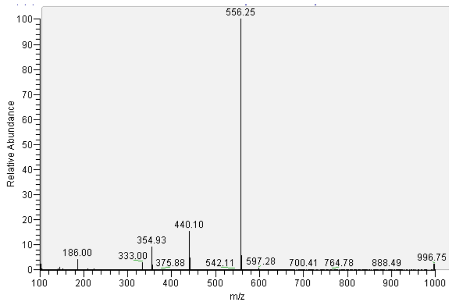


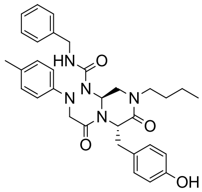




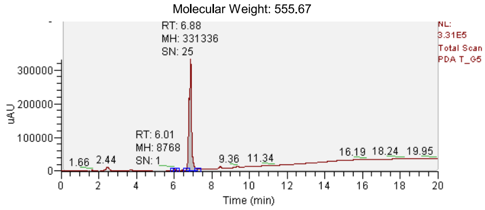
Exact Mass: 505.31
Molecular Weight: 505.65

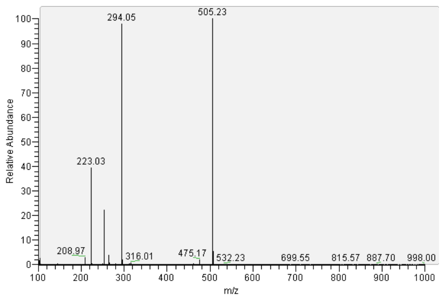


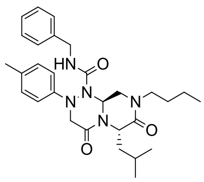




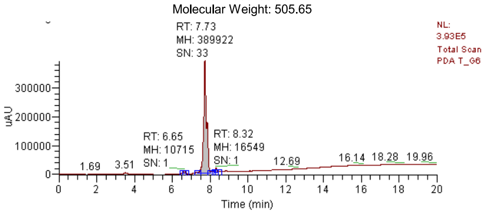
Exact Mass: 555.28
Molecular Weight: 555.67

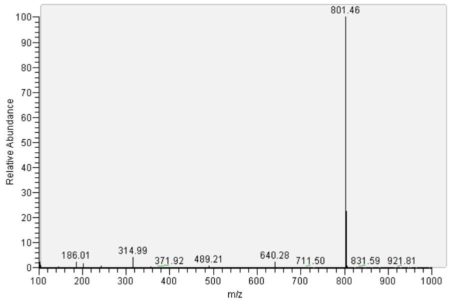


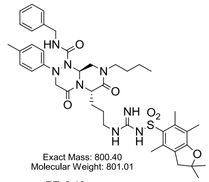


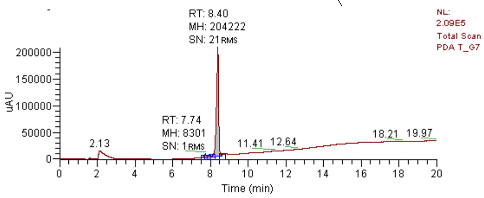


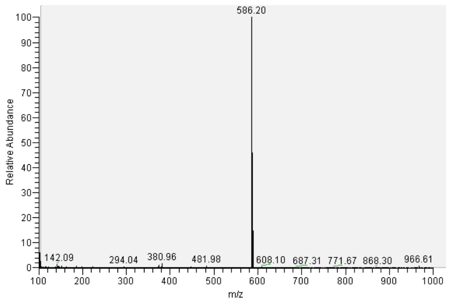
Exact Mass: 505.31
Molecular Weight: 505.65

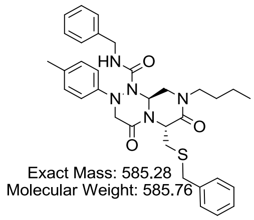


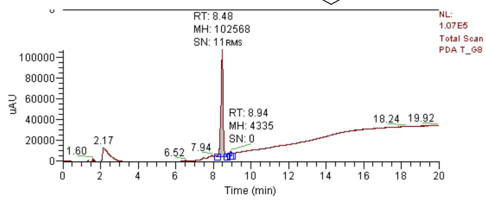

801.46
186.01
314.99
371.92
489.21
640.28
711.50
831.59
921.81
Relative Abundance
m/z


Exact Mass: 800.40
Molecular Weight: 801.01


RT: 8.40
MH: 204222
SN: 21RMS
RT: 7.74
MH: 8301
SN: 1RMS
2.13
11.41
12.64
18.21
19.97
NL:
2.09E5
Total Scan
PDA T_G7
uAU
Time (min)


586.20
142.09
294.04
380.96
481.98
608.10
687.31
771.67
868.30
966.61
Relative Abundance
m/z


Exact Mass: 585.28
Molecular Weight: 585.76


RT: 8.48
MH: 102568
SN: 11RMS
RT: 8.94
MH: 4335
SN: 0
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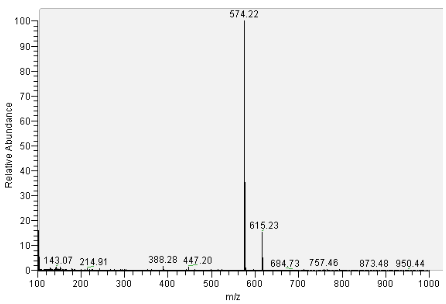
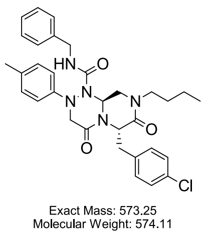
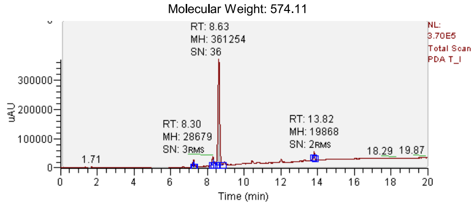
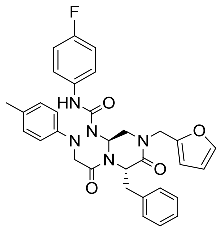
2.17
6.52
7.94
18.24
19.92
NL:
1.07E5
Total Scan
PDA T_G8
uAU
Time (min)

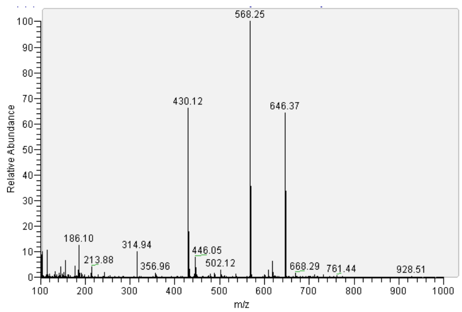

574.22
615.23
143.07
214.91
388.28
447.20
684.73
757.46
873.48
950.44
Relative Abundance
m/z

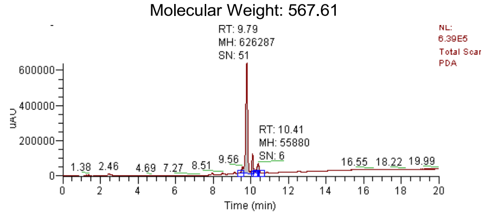

Exact Mass: 573.25
Molecular Weight: 574.11

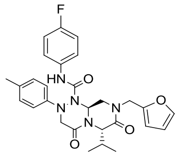

RT: 8.63
MH: 361254
SN: 36
RT: 8.30
MH: 28679
SN: 3RMS
RT: 13.82
MH: 19868
SN: 2RMS
1.71
18.29
19.87
NL:
3.70E5
Total Scan
PDA T_I
uAU
Time (min)



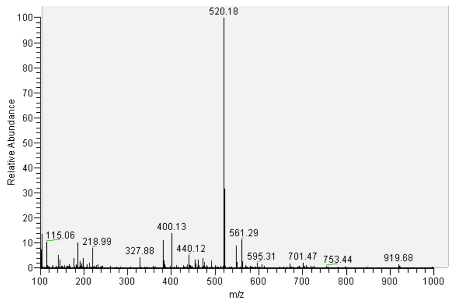
Exact Mass: 567.23
Molecular Weight: 567.61

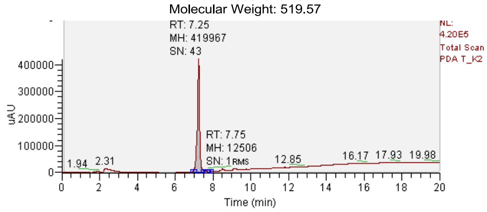


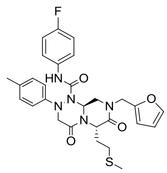




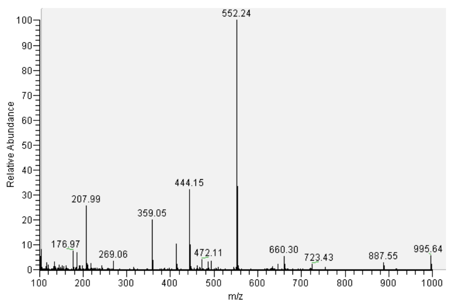
Exact Mass: 519.23
Molecular Weight: 519.57

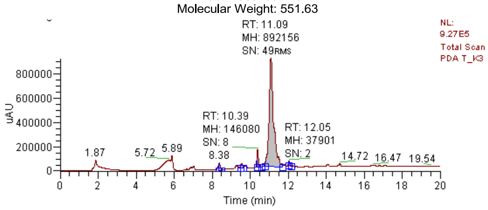


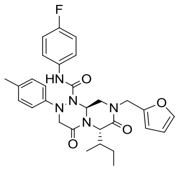




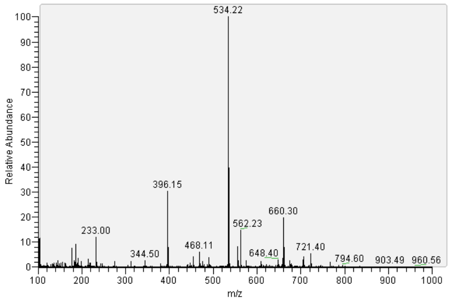
Exact Mass: 551.20
Molecular Weight: 551.63

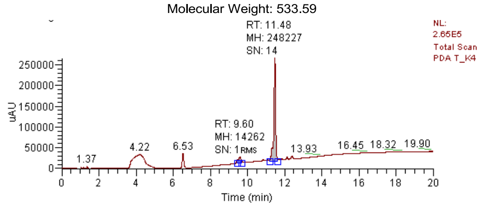


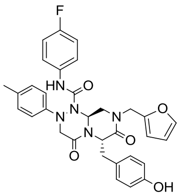




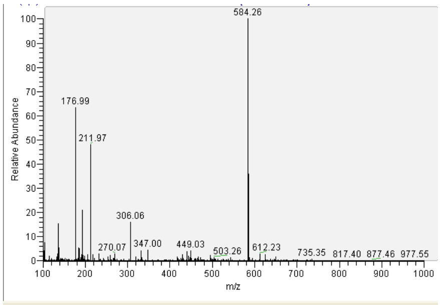
Exact Mass: 533.24
Molecular Weight: 533.59

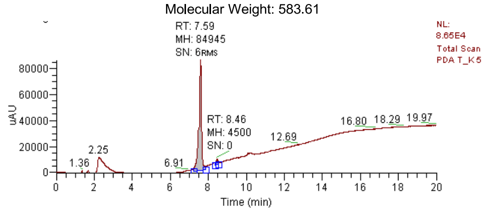


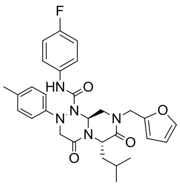




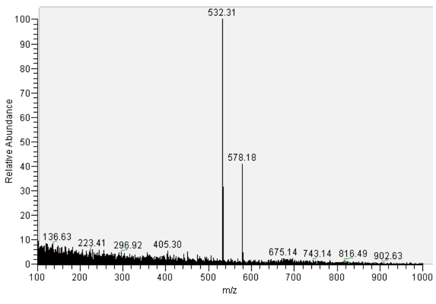
Exact Mass: 583.22
Molecular Weight: 583.61

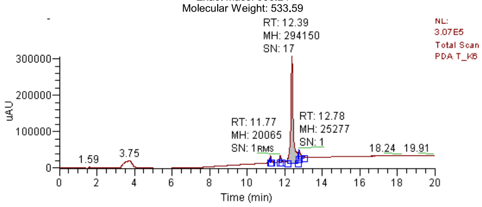


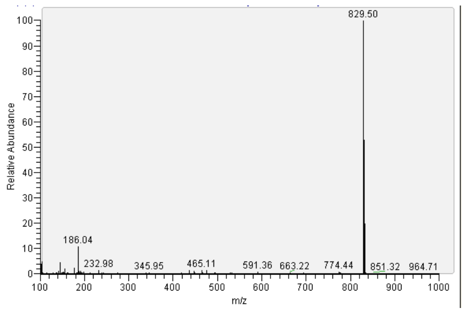




Exact Mass: 533.24
Molecular Weight: 533.59






829.50
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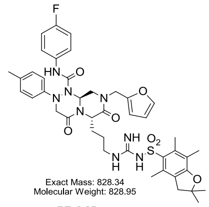
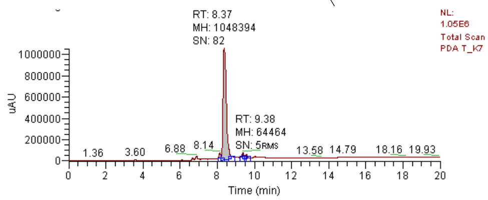
232.98
345.95
465.11
591.36
663.22
774.44
851.32
964.71
Relative Abundance
m/z


Exact Mass: 828.34
Molecular Weight: 828.95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MH: 1048394
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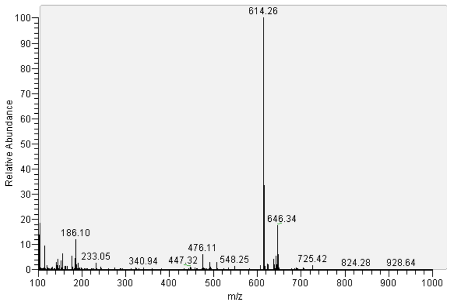
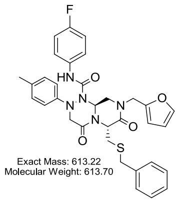
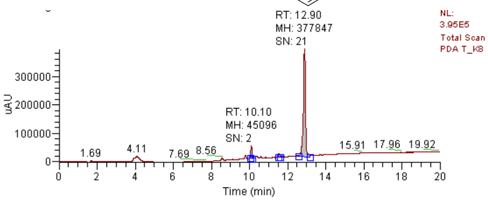
1.05E6
Total Scan
PDA T_K7
uAU
Time (min)


614.26
646.34
186.10
233.05
340.94
447.32
476.11
548.25
725.42
824.28
928.64
Relative Abundance
m/z


Exact Mass: 613.22
Molecular Weight: 613.70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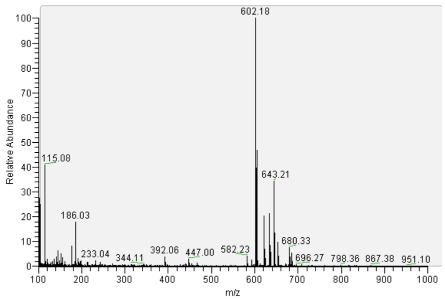
SN: 2
NL:
3.95E5
Total Scan
PDA T_K8
uAU
Time (min)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643.21
115.08
186.03
233.04
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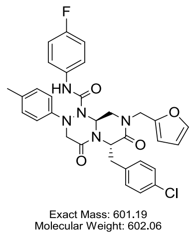
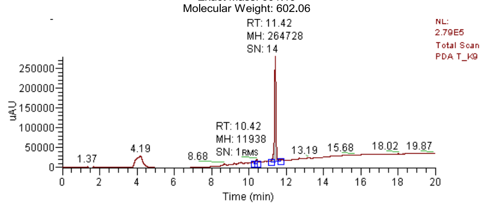
582.23
680.33
696.27
798.36
867.38
951.10
Relative Abundance
m/z


Exact Mass: 601.19
Molecular Weight: 602.06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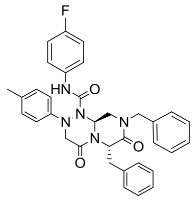
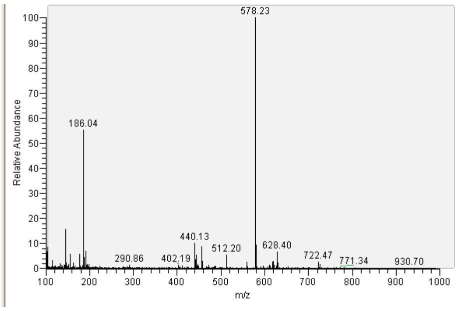
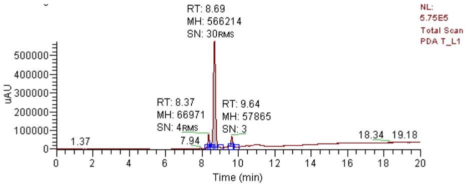
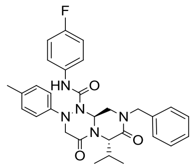
MH: 264728
SN: 14
RT: 10.42
MH: 11938
SN: 1RMS
NL:
2.79E5
Total Scan
PDA T_K9
uAU
Time (min)



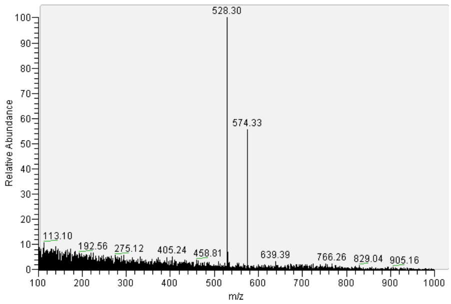
Exact Mass: 577.25
Molecular Weight: 577.65

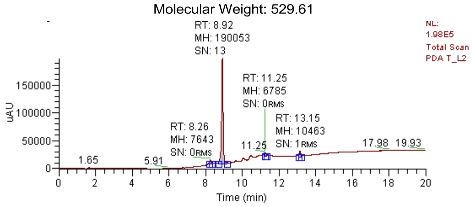


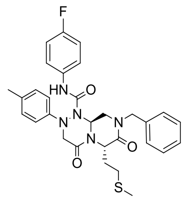




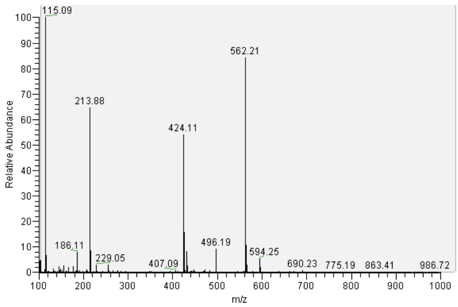
Exact Mass: 529.25
Molecular Weight: 529.61

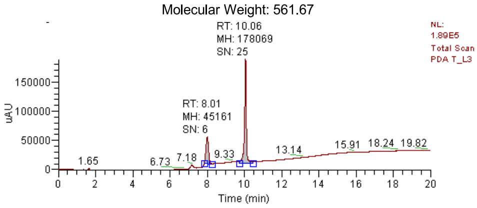


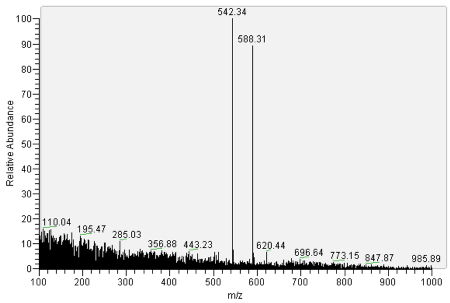


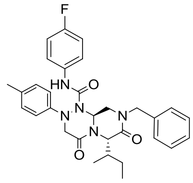


Exact Mass: 561.22
Molecular Weight: 561.67

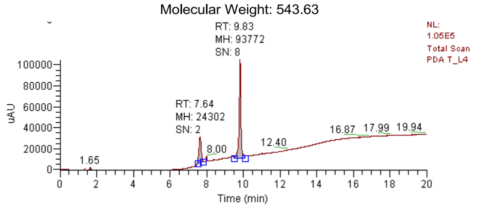


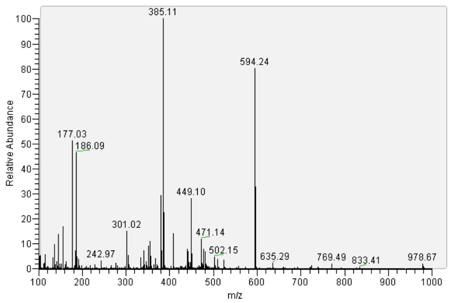


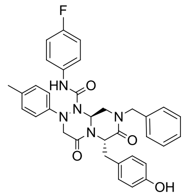




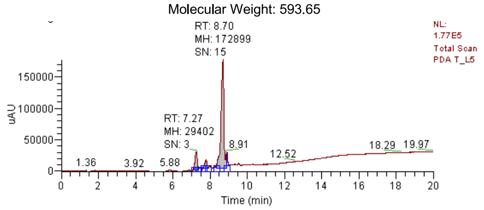
Exact Mass: 543.26
Molecular Weight: 543.63

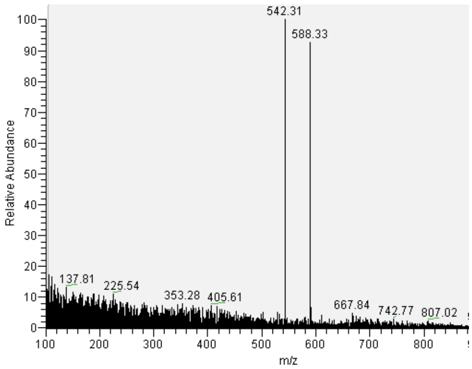


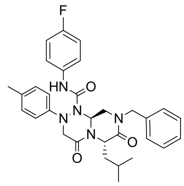




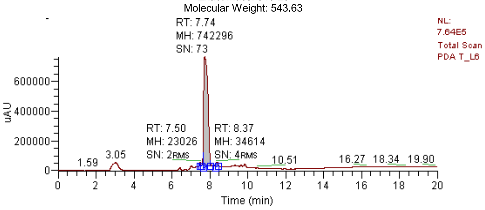
Exact Mass: 593.24
Molecular Weight: 593.65

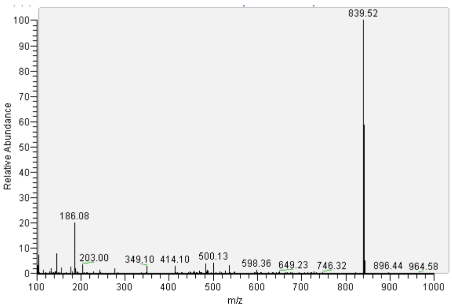


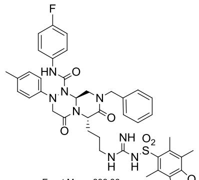




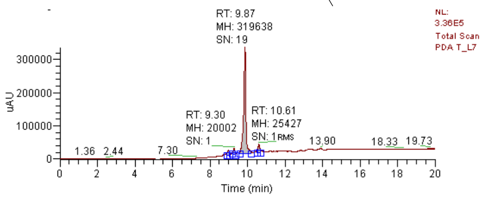
Exact Mass: 543.26
Molecular Weight: 543.63

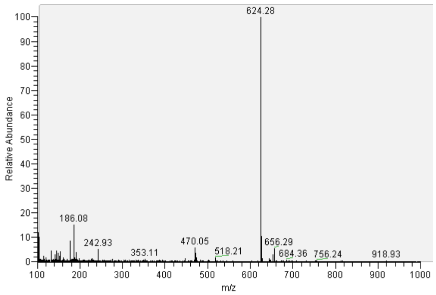


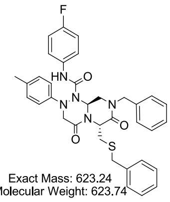




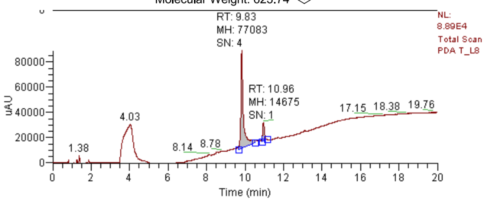
Exact Mass: 838.36
Molecular Weight: 838.99

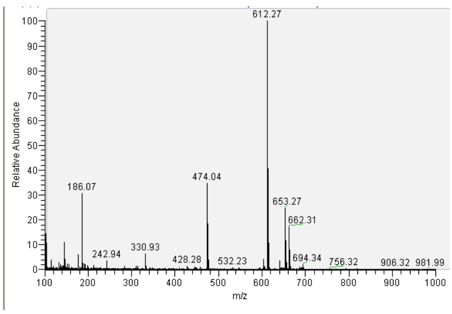


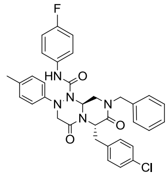




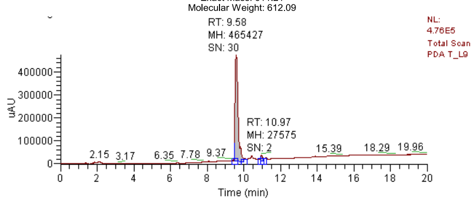
Exact Mass: 623.24
Molecular Weight: 623.74

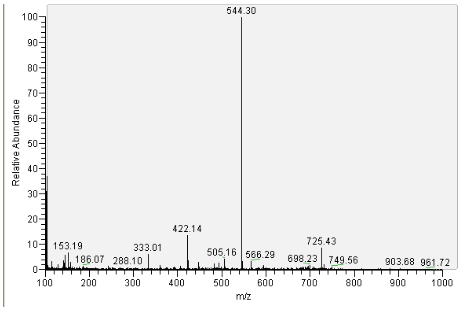


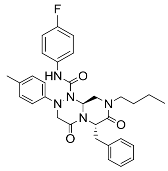




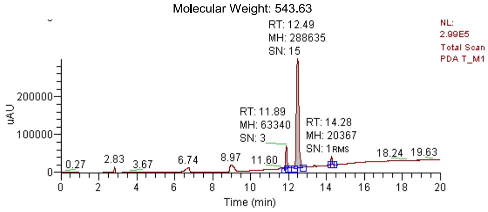
Exact Mass: 611.21
Molecular Weight: 612.09

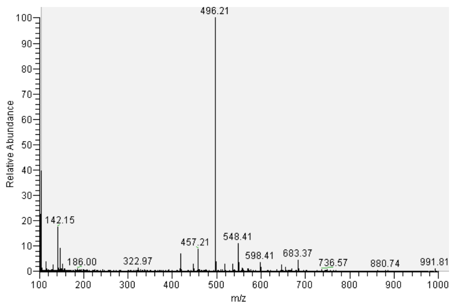


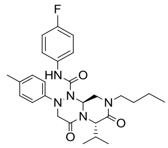




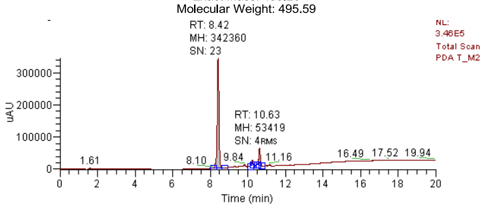
Exact Mass: 543.26
Molecular Weight: 543.63

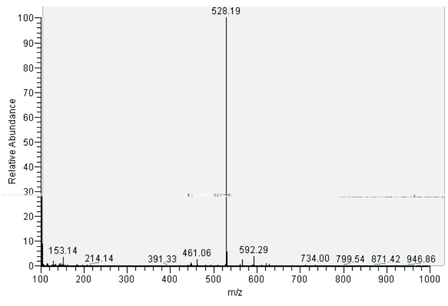


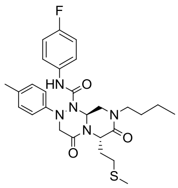




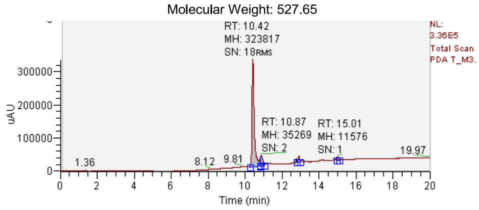
Exact Mass: 495.26
Molecular Weight: 495.59

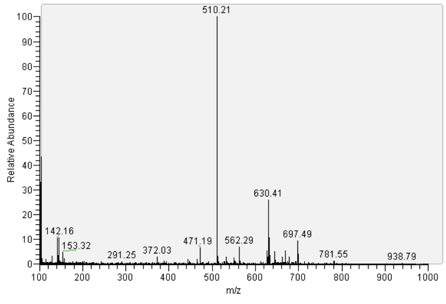


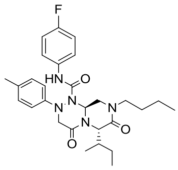




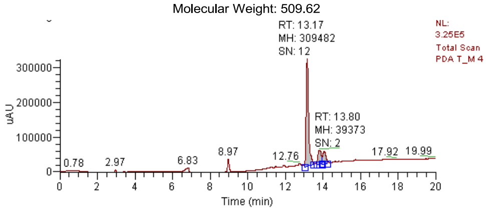
Exact Mass: 527.24
Molecular Weight: 527.65

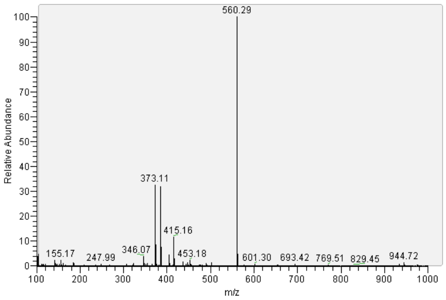


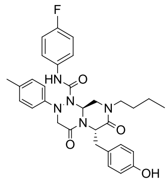




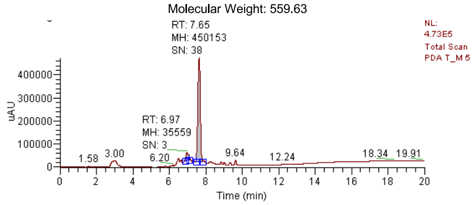
Exact Mass: 509.28
Molecular Weight: 509.62

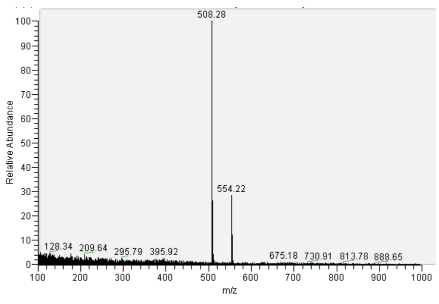


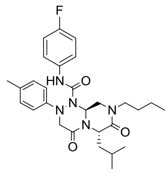




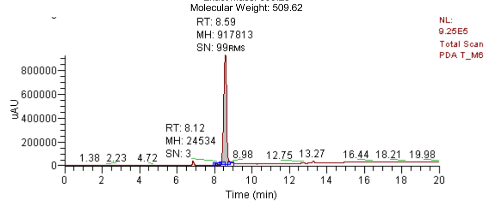
Exact Mass: 559.26
Molecular Weight: 559.63

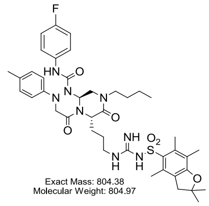


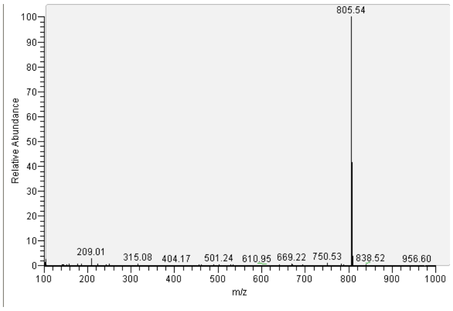


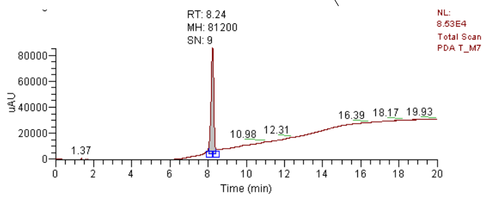


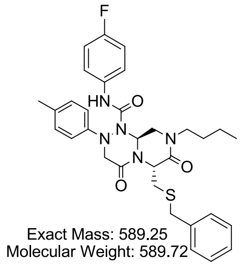
Exact Mass: 509.28
Molecular Weight: 509.62

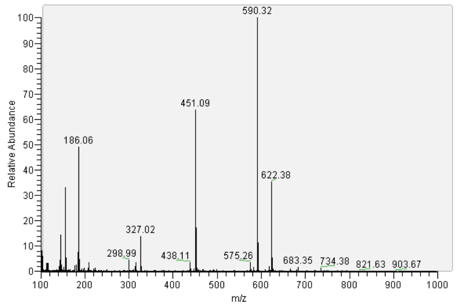


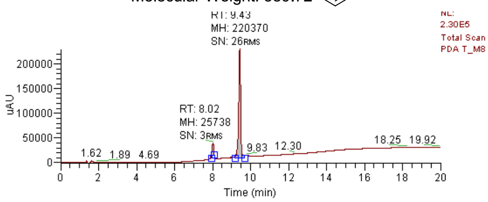

F
HN
O
N
N
N
O
O
NH
O2
S
N
H
N
H
O
Exact Mass: 804.38
Molecular Weight: 804.97


805.54
209.01
315.08
404.17
501.24
610.95
669.22
750.53
838.52
956.60
Relative Abundance
m/z


RT: 8.24
MH: 81200
SN: 9
NL:
8.53E4
Total Scan
PDA T_M7
1.37
10.98
12.31
16.39
18.17
19.93
uAU
Time (min)


F
HN
O
N
N
N
N
O
O
S
Exact Mass: 589.25
Molecular Weight: 589.72


590.32
451.09
186.06
622.38
327.02
298.99
438.11
575.26
683.35
734.38
821.63
903.67
Relative Abundance
m/z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MH: 220370
SN: 26RMS
NL:
2.30E5
Total Scan
PDA T_M8
RT: 8.02
MH: 25738
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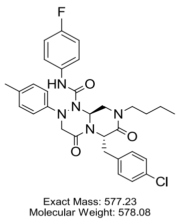
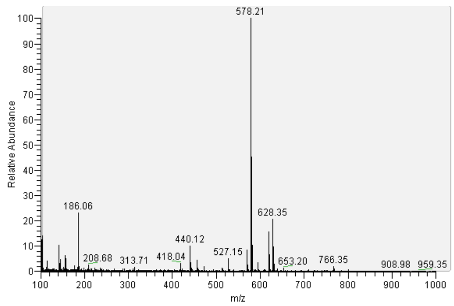
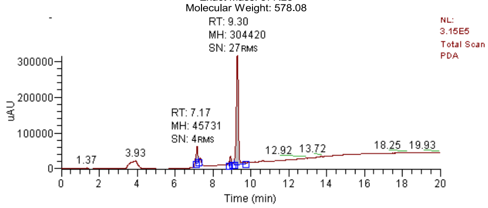
1.62
1.89
4.69
9.83
12.30
18.25
19.92
uAU
Time (min)


F
HN
O
N
N
N
N
O
O
Cl
Exact Mass: 577.23
Molecular Weight: 578.08


578.21
186.06
628.35
440.12
208.68
313.71
418.04
527.15
653.20
766.35
908.98
959.35
Relative Abundance
m/z


RT: 9.30
MH: 304420
SN: 27RMS
NL:
3.15E5
Total Scan
PDA
RT: 7.17
MH: 45731
SN: 4RMS
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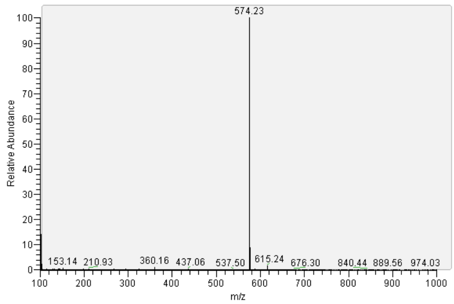
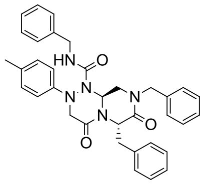
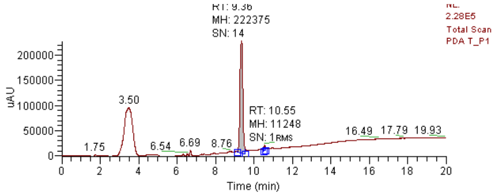
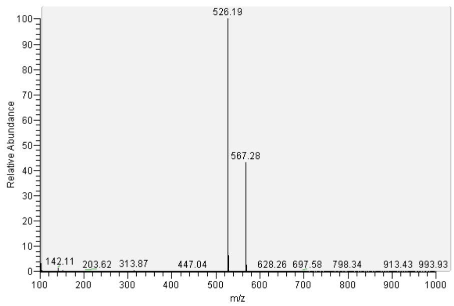
19.93
uAU
Time (min)

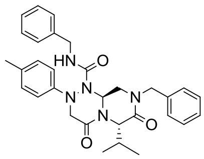




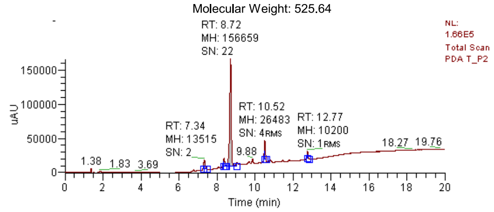
Exact Mass: 573.27
Molecular Weight: 573.68

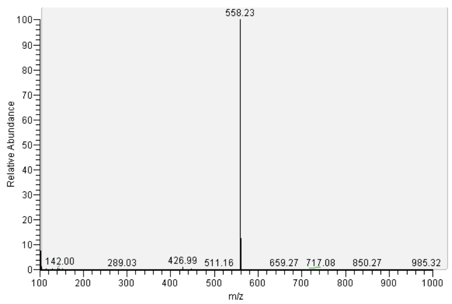


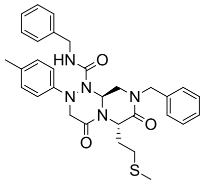




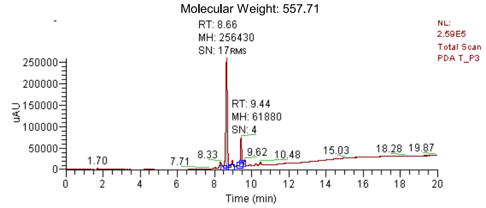
Exact Mass: 525.27
Molecular Weight: 525.64

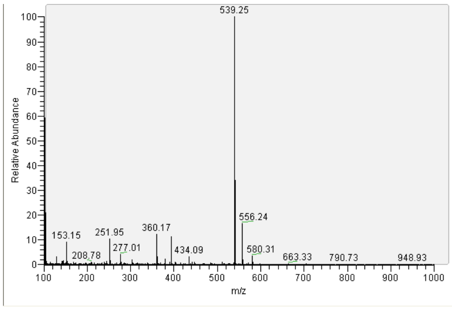


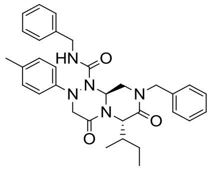




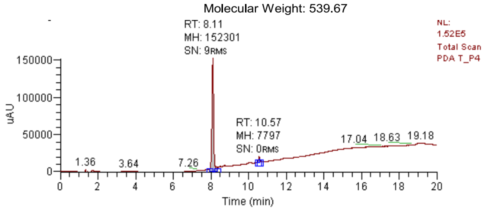
Exact Mass: 557.25
Molecular Weight: 557.71

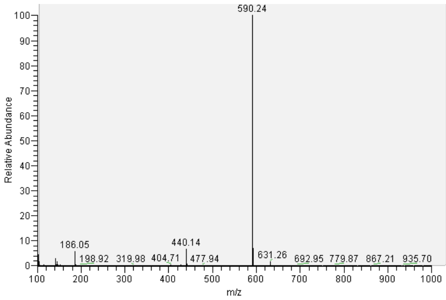


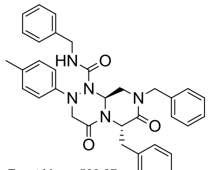




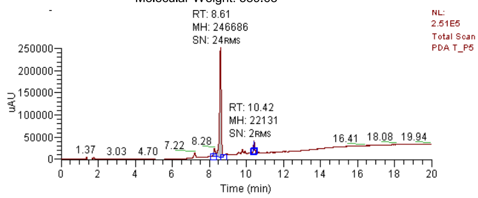
Exact Mass: 539.29
Molecular Weight: 539.67

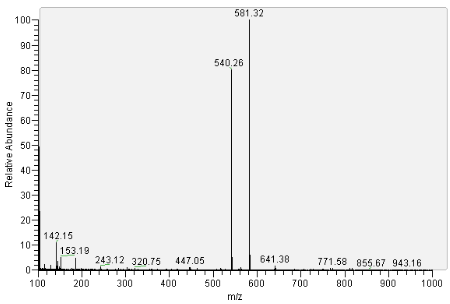


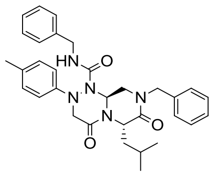




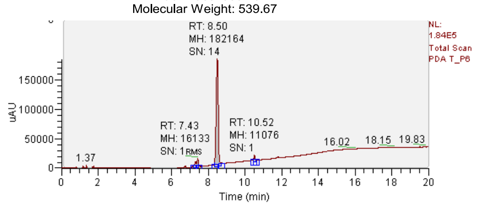
Exact Mass: 589.27
Molecular Weight: 589.68

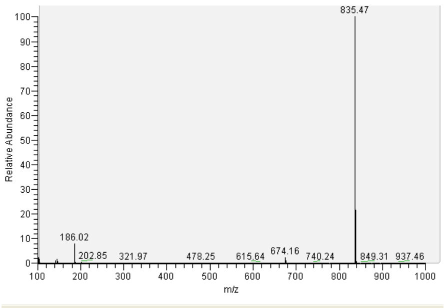


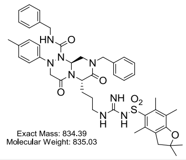




Exact Mass: 539.29
Molecular Weight: 539.67




835.47
186.02
202.85
321.97
478.25
615.64
674.16
740.24
849.31
937.46
Relative Abundance
m/z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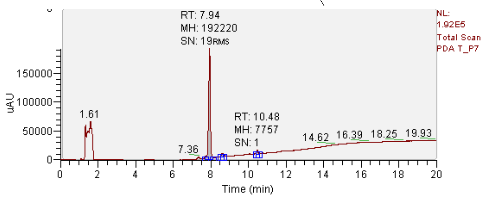
Molecular Weight: 835.03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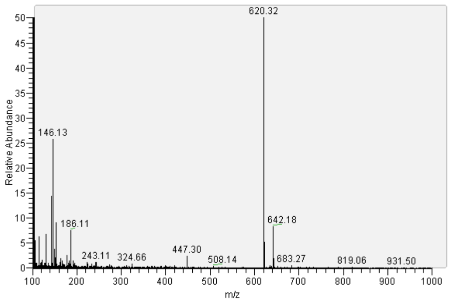
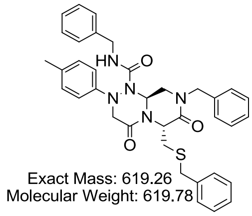
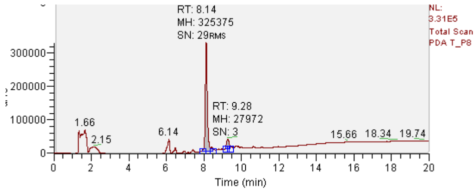
MH: 192220
SN: 19RMS
NL:
1.92E5
Total Scan
PDA T_P7
1.61
7.36
RT: 10.48
MH: 7757
SN: 1
14.62
16.39
18.25
19.93
uAU
Time (min)


620.32
146.13
186.11
243.11
324.66
447.30
508.14
642.18
683.27
819.06
931.50
Relative Abundance
m/z


Exact Mass: 619.26
Molecular Weight: 619.78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MH: 325375
SN: 29RMS
NL:
3.31E5
Total Scan
PDA T_P8
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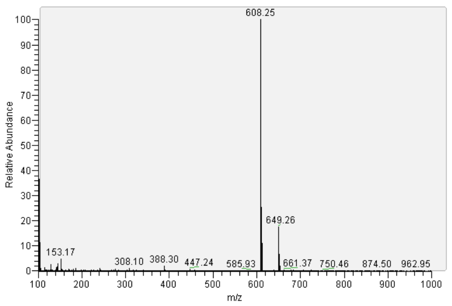
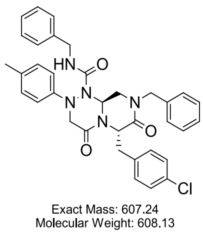
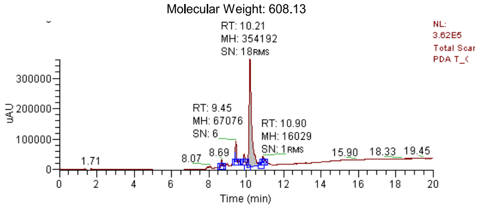
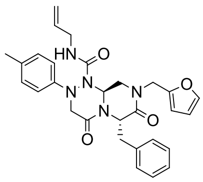
2.15
6.14
RT: 9.28
MH: 27972
SN: 3
15.66
18.34
19.74
Time (min)

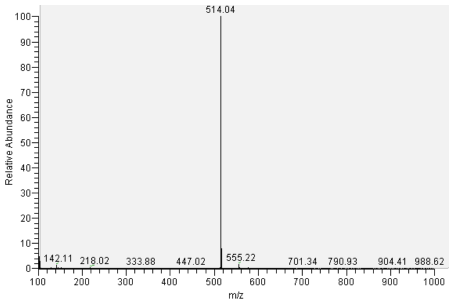

608.25
153.17
308.10
388.30
447.24
585.93
649.26
661.37
750.46
874.50
962.95
Relative Abundance
m/z

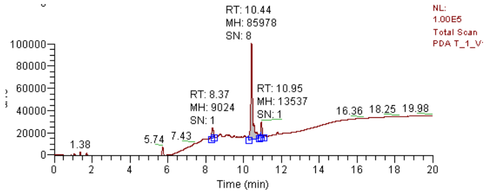

Exact Mass: 607.24
Molecular Weight: 608.13

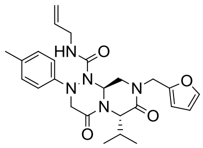

RT: 10.21
MH: 354192
SN: 18RMS
NL:
3.62E5
RT: 9.45
MH: 67076
SN: 6
RT: 10.90
MH: 16029
SN: 1RMS
1.71
8.07
8.69
15.90
18.33
19.45
uAU
Time (min)



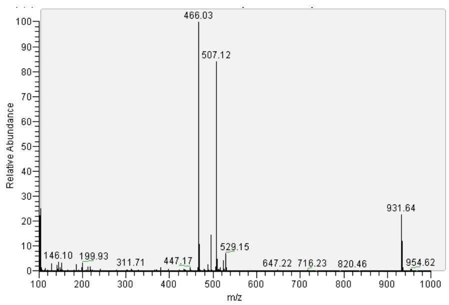
Exact Mass: 513.24
Molecular Weight: 513.59

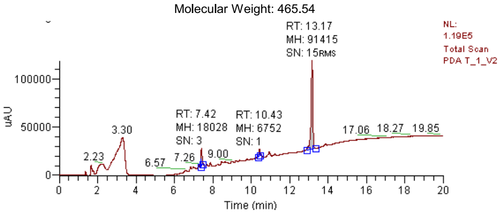


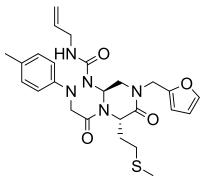




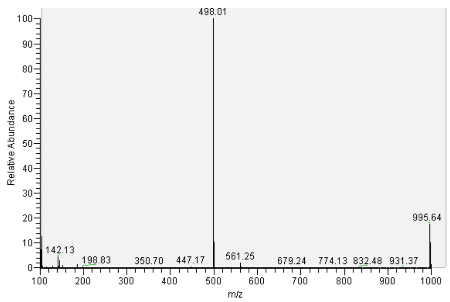
Exact Mass: 465.24
Molecular Weight: 465.54

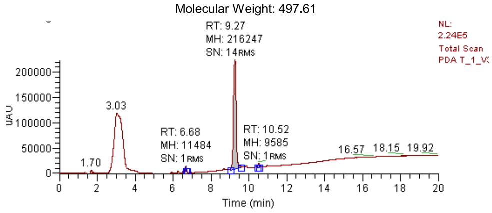


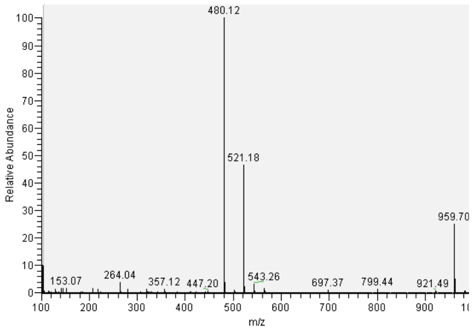


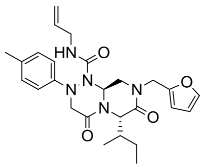


Exact Mass: 497.21
Molecular Weight: 497.61

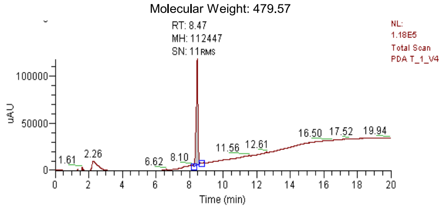


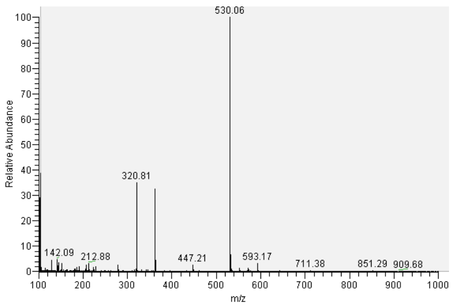


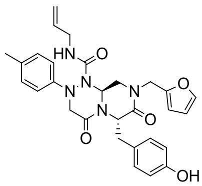




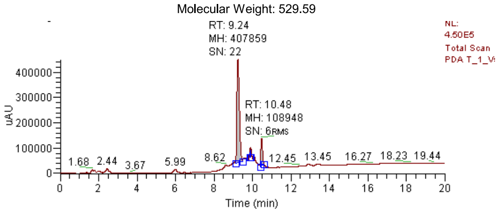
Exact Mass: 479.25
Molecular Weight: 479.57

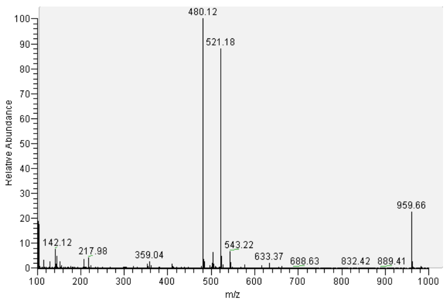


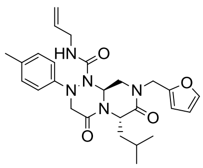




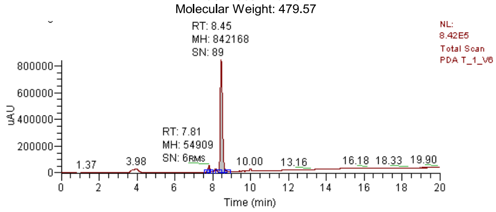
Exact Mass: 529.23
Molecular Weight: 529.59

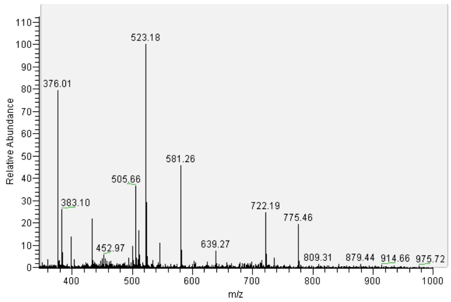


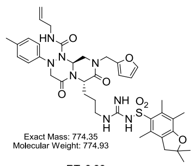


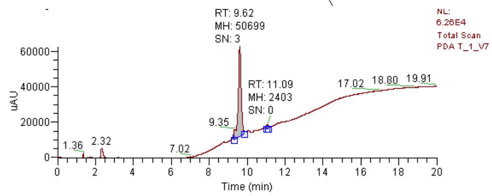


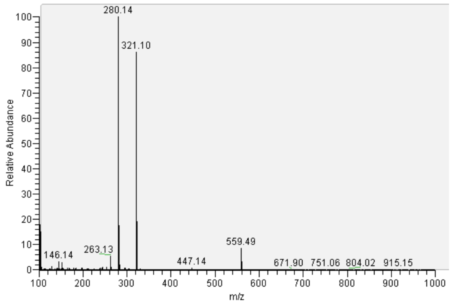
Exact Mass: 479.25
Molecular Weight: 479.57

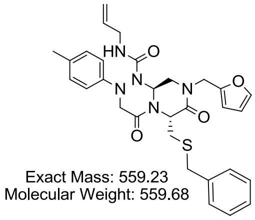


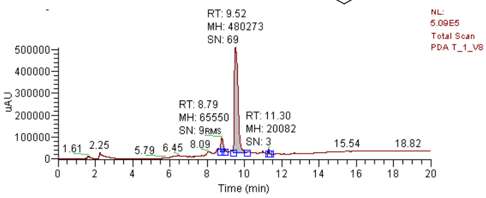


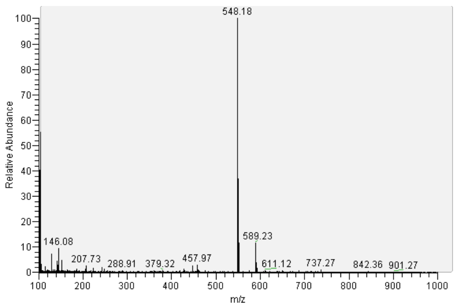


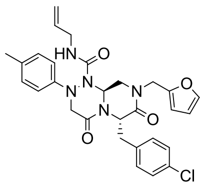




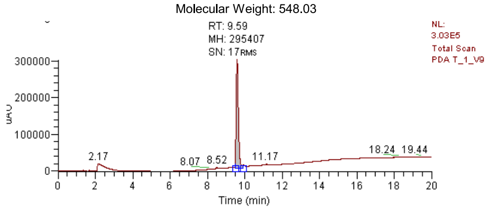


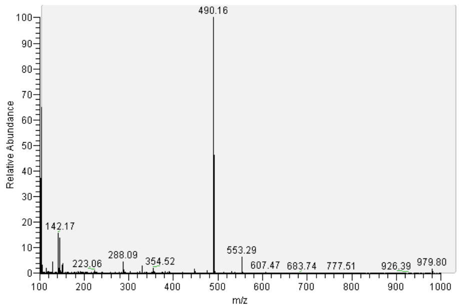


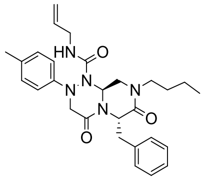




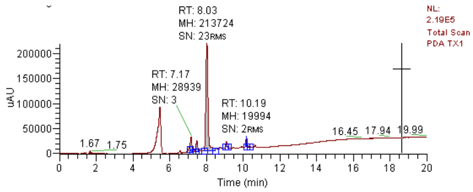
Exact Mass: 547.20
Molecular Weight: 548.03

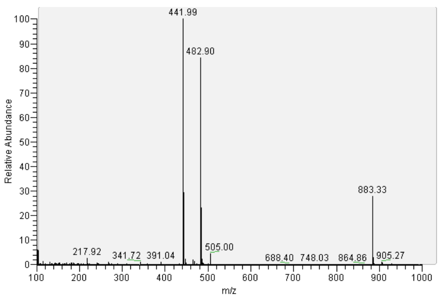


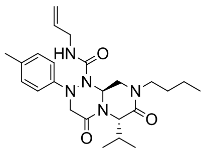




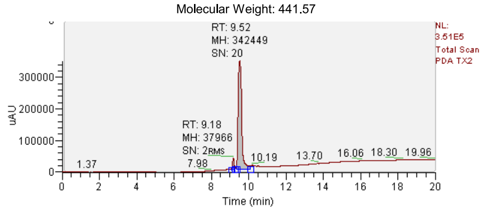
Exact Mass: 489.27
Molecular Weight: 489.61

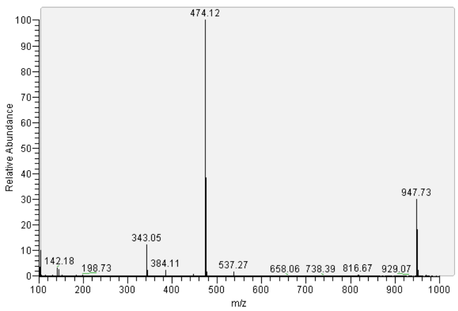


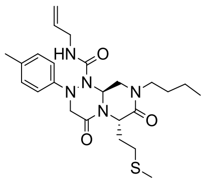




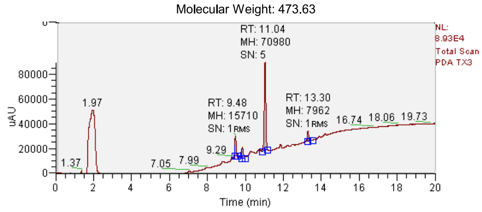
Exact Mass: 441.27
Molecular Weight: 441.57

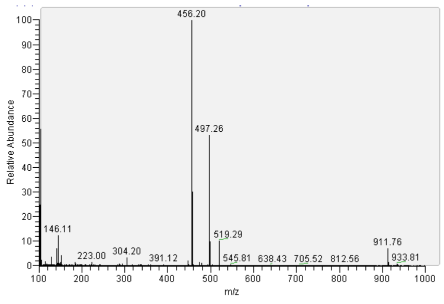


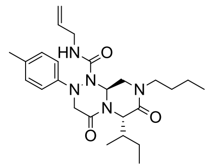




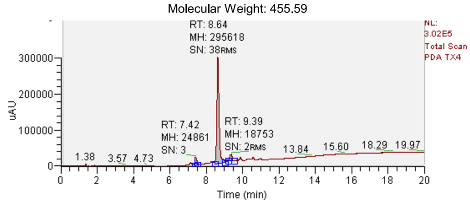
Exact Mass: 473.25
Molecular Weight: 473.63

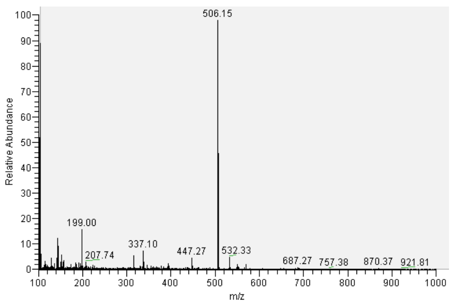


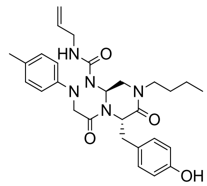




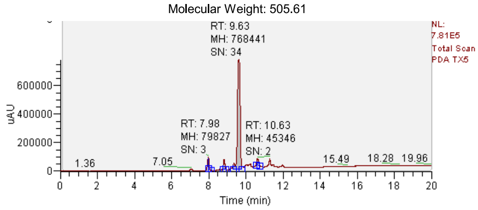
Exact Mass: 455.29
Molecular Weight: 455.59

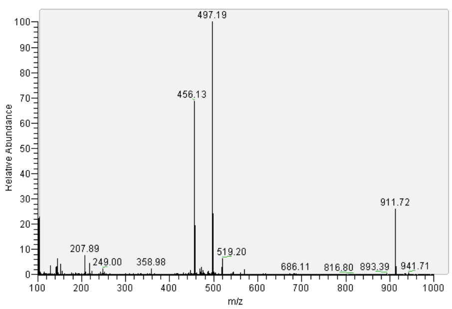


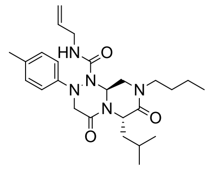




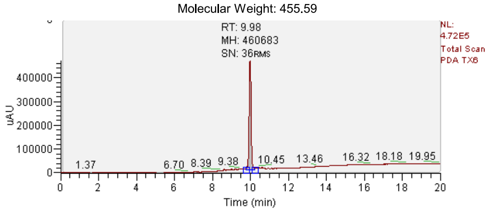
Exact Mass: 505.27
Molecular Weight: 505.61

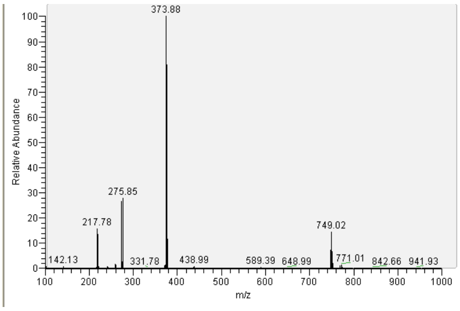


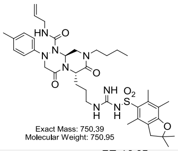


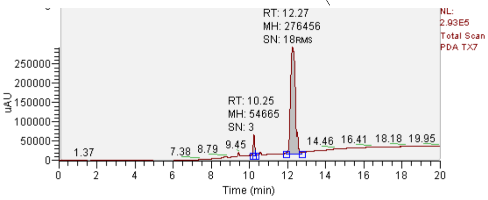


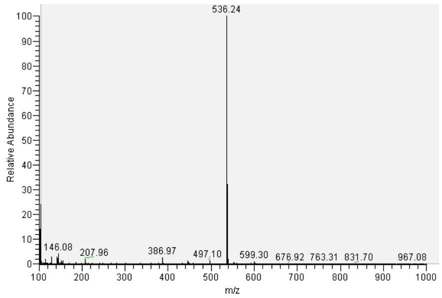
Exact Mass: 455.29
Molecular Weight: 455.59

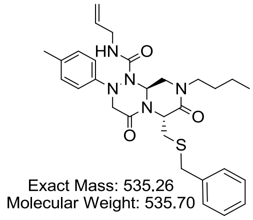


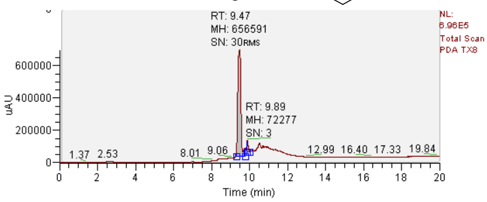


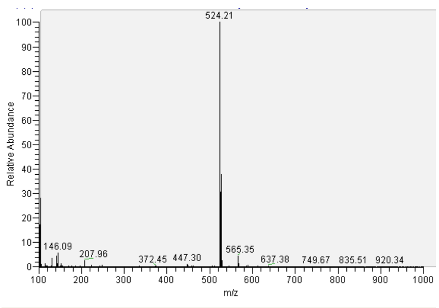


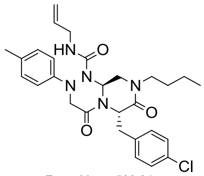


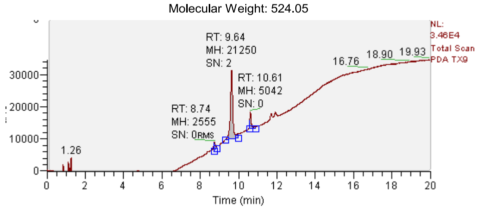


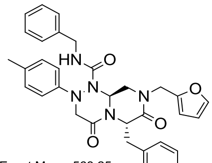




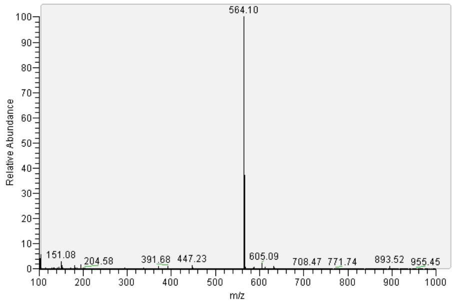


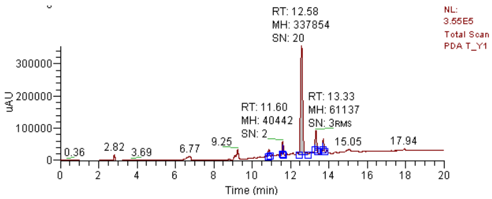

Exact Mass: 523.24
Molecular Weight: 524.05

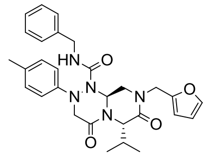




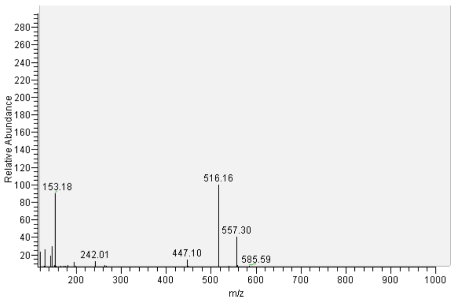
Exact Mass: 563.25
Molecular Weight:
563.65

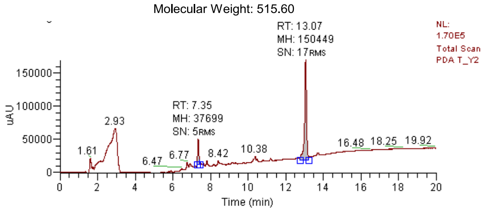


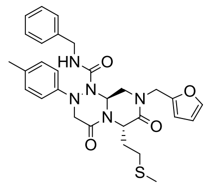




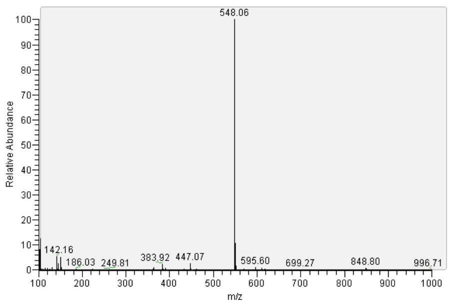
Exact Mass: 515.25
Molecular Weight: 515.60

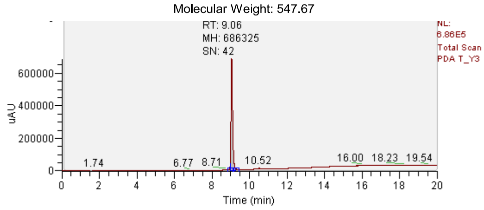


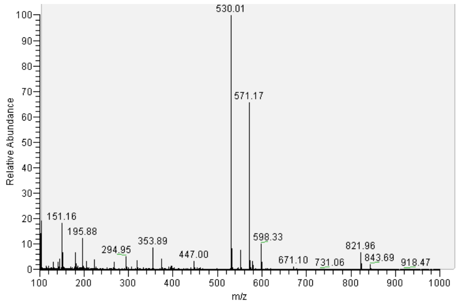


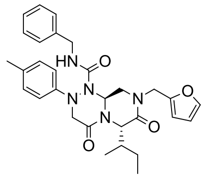


Exact Mass: 547.23
Molecular Weight: 547.67

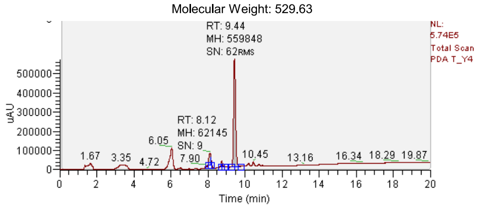


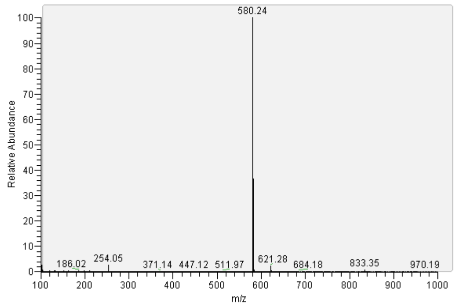


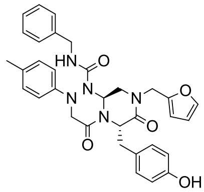




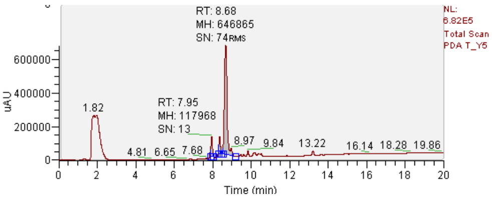
Exact Mass: 529.27
Molecular Weight: 529.63

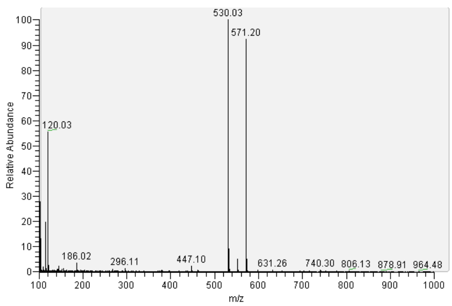


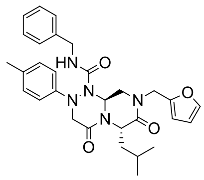




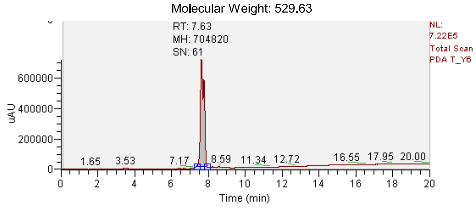
Exact Mass: 579.25
Molecular Weight: 579.65

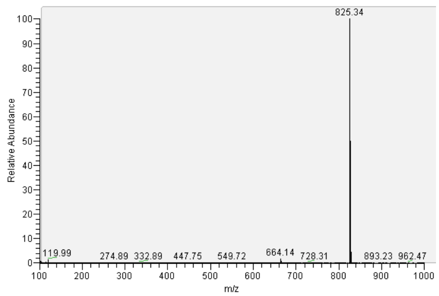


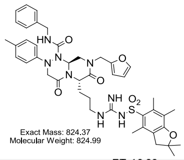


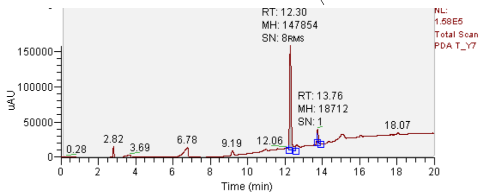


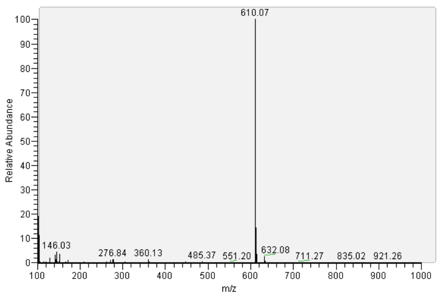
Exact Mass: 529.27
Molecular Weight: 529.63

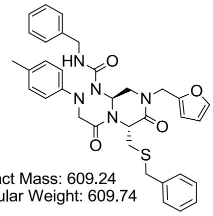


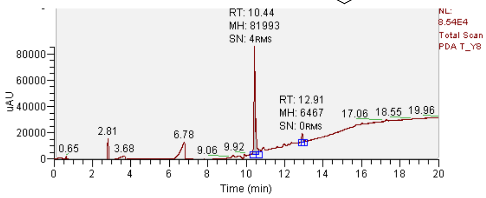


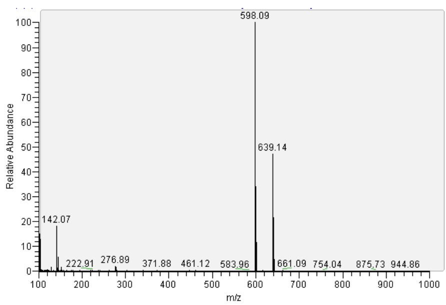


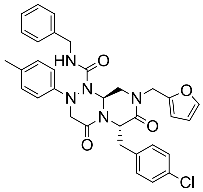





Exact Mass: 609.24
Molecular Weight: 609.74






Exact Mass: 597.21
Molecular Weight: 598.09